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TITLE: Development of a Personalized Model for Pressure Ulcer Prevention Acutely Following Spinal Cord Injury: Biomarkers of Muscle Composition and Resilience

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14. ABSTRACT Development of a pressure ulcer acutely following spinal cord injury (SCI) has a devastating impact on the progress of initial rehabilitation for too many active duty military and veterans. All persons with SCI are at increased risk of pressure ulcer development which remains one of the most significant secondary complications for these individuals. Susceptibility appears to be unique for each individual. Changes in soft tissue composition and function following SCI may provide the key to personalized risk status which the clinician can employ to determine each individual's optimal pressure ulcer prevention regime. Good risk assessment tools are currently not available to reliably identify the individual with acute SCI at risk of pressure ulcers. This project is investigating potential linkages between skeletal muscle tissue biomarkers and tissue resilience under applied loads in individuals with acute SCI at risk for pressure ulcer development. In the first six months of this observational study we have developed a framework for an objective pressure ulcer risk assessment tool to reliably identify more susceptible individuals within this high-risk population and provide the basis for personalized clinical management of tissue health. Recruitment and data collection are ongoing to collate patient data on tissue health and muscle composition.					
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1. Introduction

Development of a pressure ulcer during the acute phase following injury has a devastating impact on the progress of initial rehabilitation for too many active duty military and veterans with spinal cord injury. All persons with SCI are at increased risk of pressure ulcer development which remains one of the most significant secondary complications for these individuals. Susceptibility appears to be unique for each individual. Changes in soft tissue composition and function following spinal cord injury may provide the key to personalized risk status which the clinician can employ to determine each individual's optimal pressure ulcer prevention regime. Good risk assessment tools are currently not available to reliably identify the individual with acute spinal cord injury at risk of pressure ulcers. This project will investigate potential linkages between skeletal muscle tissue biomarkers and tissue resilience under applied loads in individuals with acute spinal cord injury at risk for pressure ulcer development. This observational study will develop an objective pressure ulcer risk assessment tool to enable clinicians to reliably identify more susceptible individuals within this high-risk population and provide the basis for personalized clinical management of tissue health.

2. Keywords

Spinal cord injury, pressure ulcer prevention, biomarkers, personalized healthcare

3. Accomplishments

Major Project Goals

Task 1: Subject Recruitment and Data Collection: Activity dates: months 1-36,
Percentage completion: 17%

Task 2: Assay and analysis of muscle composition biomarkers: Activity dates: months 1-36
Percentage completion: 22%

Task 3: Development of pressure ulcer risk predictive model: Activity dates: months 1-36
Percentage completion: 20%

Task 4: Data Analyses and Report Writing Activity dates: months 6-36,
Percentage completion: 15%

Accomplishments under these goals

Task 1: Subject Recruitment and Data Collection: Activity dates: months 1-36,

1) Major activities:

a) *Local Institutional Review Board (IRB) and DoD Human Research Protection Office (HRPO) approvals*

All regulatory approvals have been received and are current. *Approved as of 09/30/15*

b-d) *Subject Recruitment and Data Collection*

Baseline CT/muscle biopsy & tissue health assessments have been completed for 2 subjects.

Tissue health questionnaires are being administered weekly (see Task 3c)

In progress

2) Specific objectives

Forty individuals with complete or incomplete SCI within 6 months of injury will be recruited: Recruitment will be stratified to achieve a study cohort that includes participants with and without a history of acute PU. Exclusion criteria will include having an open pelvic region pressure ulcer at the time of recruitment and/or known sensitivity to contrast. Pelvic region CT scans with contrast will be carried out following the standardized protocol developed in our previous work. Contrast-free CT scans of the glutei for individuals with high (greater than 75%) or low (less than 10%) intramuscular fat in each sub-group will also be obtained. Gluteal region tissue health will be monitored using our established protocol, specifically tissue oxygenation and blood flow will be monitored using transcutaneous oxygenation and laser Doppler blood techniques. Muscle perfusion will be monitored using near-infra red spectroscopy (NIRS). Tissue health assessments will be carried out in unloaded and supine postures at recruitment. CT scanning and tissue health assessment in unloaded and sitting postures will be obtained once the individual is fully remobilized, and will be repeated annually during the course of the study.

3) Significant results

Nothing to Report

4) Other achievements

Nothing to Report

Task 2: Assay and analysis of muscle composition biomarkers: Activity dates: months 1-36

1) Major activities:

a) *Development of Case Report Forms for collection of deidentified muscle composition data*

Electronic versions of CRF for muscle composition data collection have been constructed and reviewed by the study team, in particular Dr Alvarado (radiologist) and Dr Sun (biostatistician). The electronic CRF has limited allowed fields for data entry which will prevent errors in study data collection to provide a reliable data source for preliminary model development. *Completed 01/27/15*

b) *Obtain baseline muscle biopsy tissue and plasma from study participants*

Baseline muscle tissue biopsy and blood collections have been completed for two study participants. *In progress*

2) Specific objectives

Circulatory biomarkers associated with muscle composition will be assessed using plasma collected from study participants. Biomarkers involved in fatty metabolism will be assessed at gene and protein levels using quantitative RT-PCR (qRT-PCR) and Western blotting respectively. Local muscle biopsy tissue will be evaluated using the same techniques together with immunohistochemistry to determine localized biomarkers.

3) Significant results

Nothing to Report

4) Other achievements

Nothing to Report

Task 3: Development of pressure ulcer risk predictive model: Activity dates: months 1-36

1) Major activities:

a) *Development of Case Report Forms for deidentified data collection.*

Electronic versions of CRF for study participant intake and tissue health data collection were constructed and reviewed by the study team, including Dr Richmond (SCI physician), Dr McDaniel (health scientist) and Dr Sun (biostatistician). The electronic CRF has limited allowed fields for data entry which will prevent errors in study data collection to provide a reliable data source for preliminary model development. *Completed 01/27/15*

b) *Define model structure and implement preliminary model*

The data collected in the CRF will inform the model structure. Consistent data entry will be important so that all data can be analyzed directly from the electronic database. The basic structure of the model has been defined based on the CRF developed on 2(a) and 3(a).

In progress

c) *Study participant follow-up: Short questionnaire format data will be collected from enrolled patients weekly.*

We have developed a 9 item questionnaire which is available via Google docs (<http://goo.gl/forms/fy0QRZ2QKK>) for participants to check in weekly online once discharged. We also contact participants by phone every week because some do not like to use the Internet.

In progress

2) Specific objectives

A multivariate model of pressure ulcer risk based on muscle composition will be developed based on the tissue health variables and biomarkers assessed under Tasks 1 and 2. Study participants will be followed weekly following recruitment and assessment to determine tissue health status. Incidences of tissue compromise or breakdown will be monitored and data applied to refine the risk model.

3) Significant results

Nothing to Report

4) Other achievements

Nothing to Report

Task 4: Data Analyses and Report Writing Activity dates: months 6-36,

1) Major activities:

a) Preliminary analysis and initial manuscripts.

In progress

2) Specific objectives

Analysis of project data will validate the original study hypotheses and provide the basis for reliable PU risk assessment acutely following SCI. A predictive model based on muscle composition biomarkers and tissue health assessment will be developed to facilitate personalized PU prevention programs, including pressure relief regimes and selection of support surfaces, to optimize tissue health during initial rehabilitation. Study findings will be presented at local and national meetings and published in the peer-reviewed literature.

3) Significant results

Nothing to Report

4) Other achievements

Nothing to Report

Discussion of stated goals not met

Recruitment during the first 6 months of approval for this project has been slower than desired. Unfortunately, many Veterans admitted to our facility acutely following SCI already have tissue breakdown on admission. This often does not fully resolve within 6 months of injury, which has limited enrollment under the current study inclusion criteria.

We would like to note that at our recent team meeting, 4 eligible candidates for the study were identified however enrollment was not complete at the time of this report.

Opportunities for training and professional development

Nothing to Report

Dissemination to communities of interest

We have conducted outreach activities to inform members of our local communities about the study we are conducting. These activities have included outreach to Veterans and non-veterans with spinal cord injury, and professionals involved in the care of individuals with SCI. Outreach activities are listed below:

Cleveland VA Research Week May , 2015
Study personnel presented a poster to let Veterans know about our study.

35th Annual National Veterans Wheelchair Games, Dallas, TX June 21-26, 2015
Study coordinator, Ms. Graebert attended the games as a volunteer and spoke to many Veterans both within the Ohio region and nationally about our study.

MetroHealth Rehabilitation Institute of Ohio 20th Annual SCI Forum Sept , 2015
The study team attended the Forum and spoke to many individuals with SCI and clinicians about our study. We were also contacted by the local National Spinal Cord Injury Association director who would like us to come and talk to his group.

In addition to these external outreach meetings we have presented information on our study to inform clinicians at LSCDVAMC about our study at interactive lunch-and-learn sessions with SCI/D physicians, therapists and outpatient service personnel.

Plans for next reporting period to accomplish project goals

Task 1: Subject Recruitment and Data Collection:

- Continue recruitment of patients admitted to the SCI/D unit of the LSCDVAMC with acute spinal cord injury of less than 6 months duration.
- Expand recruitment criteria to include veterans who have already been discharged and non-veterans at other local facilities in the Cleveland Metro region.
- Continue to obtain baseline pelvic CT scans with contrast following our established protocol.
- Continue to obtain baseline tissue health assessments.

Task 2: Assay and analysis of muscle composition biomarkers:

- Continue to obtain baseline muscle biopsy tissue and plasma from study participants.
- Assay muscle tissue and plasma using quantitative rt-PCR and Western blotting.
- Assay baseline muscle tissue samples using immunohistochemical staining.

Task 3: Development of pressure ulcer risk predictive model:

- Continue to develop and test electronic database based on CRF data collection structure to provide reliable data source for preliminary model.
- Continue weekly collection of skin status using short form questionnaire

Task 4: Data Analyses and Report Writing:

- Draft initial manuscript

4. Impact

Impact on the development of the principal discipline(s) of the project

Nothing to Report

Impact on other disciplines

Nothing to Report

Impact on technology transfer

Nothing to Report

Impact on society beyond science and technology

Nothing to Report

5. Changes/Problems

Changes in approach and reasons for change

Due to the slow recruitment during the first 6 months of approval, we are expanding our recruitment pool to include non-Veterans. As we proposed on our pre-award response to SOGOR (Aug 2014), we have already reached out to colleagues locally to investigate the possibility of multi-center recruitment. This has included other centers within the Cleveland area, specifically MetroHealth Medical Center, which is the largest Level I adult trauma and burn center in northern Ohio, and the Cleveland Clinic Foundation. An IRB modification request is currently in review.

Actual or anticipated problems or delays and actions or plans to resolve them

Please see above – due to slow recruitment during the first 6 months of approval, we are submitting a modification to expand enrollment to non-veterans. This will enlarge the pool of potential participants but will not otherwise change the study procedures in any way.

Changes that had a significant impact on expenditures

The changes outlined above were in progress toward the end of the report period. Expenditure has been reduced during the first 6 months of approval due to the slow initial recruitment.

Significant changes in use or care of human subjects

Nothing to Report

6. Products

Nothing to report

7. Participants & Other Collaborating Organizations

Individuals who have worked on the project

Name: Kath Bogie
Project Role: PI
Researcher Identifier: 0000-0003-1020-9695(ORCID ID)
Nearest person month worked: 1
Contribution to Project: No change

Name: Jennifer Graebert
Project Role: Study Coordinator
Researcher Identifier: N/A
Nearest person month worked: 1
Contribution to Project: No change

Name: Tykie Theofilos
Project Role: Research Assistant
Researcher Identifier: N/A
Nearest person month worked: 1
Contribution to Project: No change

Changes in active other support of the PI since the last reporting period

Dr Kath Bogie (PI)

Studies ended 09/30/14 -09/30/15

Ended 09/30/15: VA Rehabilitation and Research Development Service Merit Award
Effort: 2.4 cal months
Development of a low-cost advanced modular pressure relief cushion

Ended 06/30/15: NIH Innovator Program, Office of the Director
PI: Lavik E, Case Western Reserve University
Effort: 1.2 cal months (Co-Investigator)
Clinically translatable nanotechnology: hemostasis and neuroprotection

New studies 09/30/14 -09/30/15

Started 01/01/15: Craig H. Neilsen Foundation
Effort: 1.8 cal months
Development of a personalized pressure ulcer /deep tissue injury risk tool for chronic SCI

Started 05/01/15: VA SPIRE Program

PI: McDaniel J, Cleveland VA Medical Center

Effort: 1.2 cal months (Co-Investigator)

Exercise to improve blood flow and vascular health in the lower limbs of SCI

Started 09/30/15: Spinal Cord Injury Research Program, Dept of the Army CDMRP

Effort: 2.4 cal months

Toward personalized pressure ulcer care planning: development of a bioinformatics system for individualized prioritization of clinical practice guidelines

Other organizations involved as partners

Organization Name: Case Western Reserve University

Location of Organization: Cleveland, Ohio

Partner's contribution to the project: Collaboration & Facilities

8. Special Reporting Requirements

Not applicable

9. Appendices

Not applicable