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TITLE: Assessing Biomechanical Function and Hip-Stabilizing Muscle Quality Associated with Transfemoral Osseointegration

PRINCIPAL INVESTIGATOR: Dr. Jeannie Bailey, PhD

CONTRACTING ORGANIZATION: University of California, San Francisco

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**14. ABSTRACT**

In order to assess the walking mechanics and effects on hip function that accommodate lower limb osseointegrated prosthetics, we propose a study comparing walking mechanics from motion analysis and hip muscle health from MRI between osseointegrated and socket transfemoral amputees who are at least two years following final surgery with no outstanding complications. Results from this work stand to 1) report the biomechanical outcomes of lower limb osseointegrated prosthetics in comparison to conventional socket prosthetics, 2) clarify the role of muscle function on biomechanical outcomes in lower limb amputees and explore the related risk for hip replacement on the affected side for transfemoral osseointegration, 3) inform targeted rehabilitation approaches for improving walking mechanics, and 4) motivate the development of regenerative therapeutics for muscle recovery.

**15. SUBJECT TERMS**

NONE LISTED

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## 1. Introduction

This work seeks to explore biomechanical function associated with osseointegrated prosthetics compared to conventional socket prosthetics. We aim to understand the biomechanical outcomes of lower limb osseointegrated prosthetics in comparison to conventional socket prosthetics and clarify the role of muscle degeneration and function on compensatory gait behaviors in lower extremity amputees. We intend use results from this study to guide safe rehabilitation and mitigate risk for hip replacement.

## 2. Keywords

Osseointegration, transfemoral amputation, muscle fat infiltration, hip stability, biomechanics, MRI

## 3. Accomplishments

**What were the major goals of the project?**

Aim 1: Establish whether there are differences in gait and biomechanical function between osseointegrated and conventional socket unilateral transfemoral amputees.

Aim 2: Examine asymmetry of hip stabilizing muscle quality using advanced MRI sequences and compare with outcomes for gait and biomechanical function.

**What was accomplished under these goals?**

We are finishing the fourth quarter of Year 3 (NCE) to report progress on. Thus far, we have:

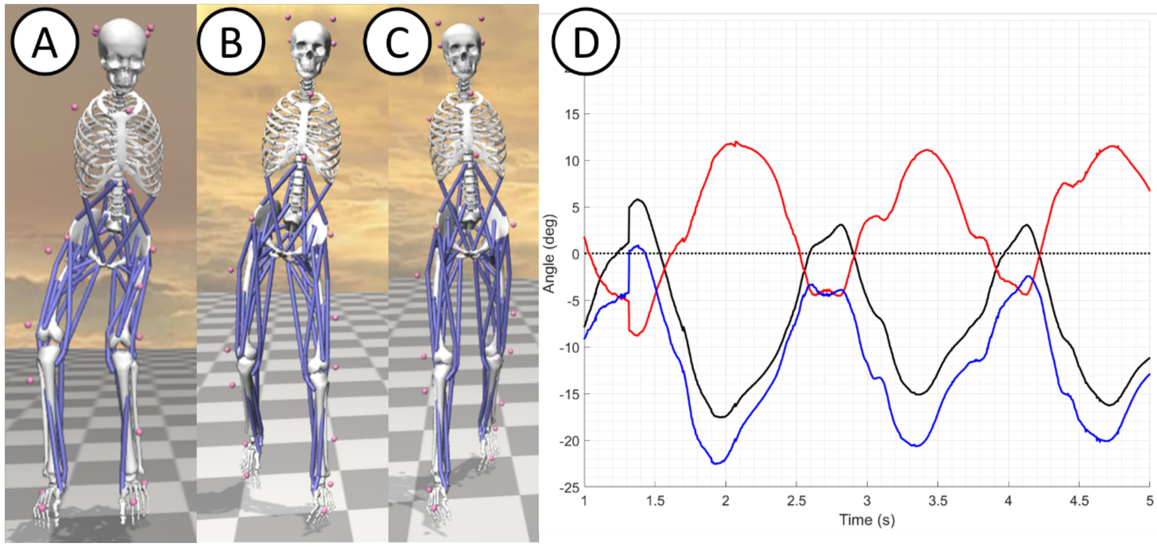
1) Subject enrollment: for osseointegration subjects, we have enrolled n=7 subjects and 5 healthy controls.

2) For biomechanical assessments in Aim 1:

   a. **Estimating muscle force from motion**

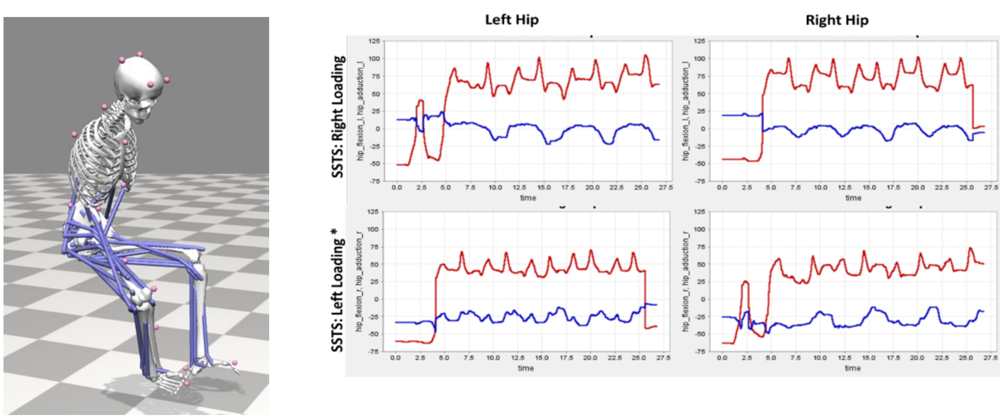
      Based on analysis of intial biomechanical data, we have finalized our biomechanical testing protocol to have repeated staggered sit to stand assessment (with Kinect) before and after up to 10 minutes of walking (or until they choose to stop due to discomfort). In addition sit to stand assessments will be completed on a force-plate.

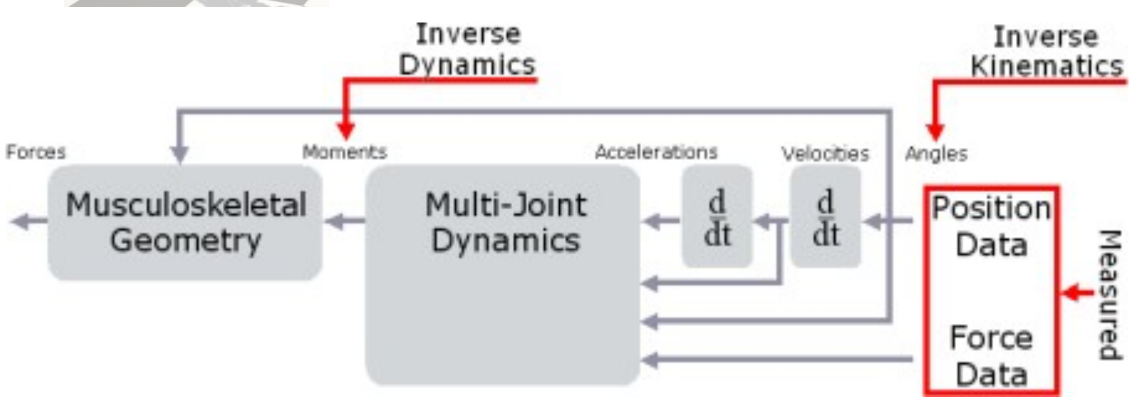
      1. To date we have been performing kinematic and dynamic analysis of subjects performing self-paced gait and sit-to-stand. Representative results from this analysis are presented in the figure below. From this analysis, we have identified persistent pelvic and hip asymmetry, increasing the loads on the intact side hip. In sit-to-stand, these compensation is likely due to the standing action being dominated by the intact side, requiring additional pelvic list to raise the prosthetic side. In gait, this pelvic list also appears during the swing phase on the prosthetic side. This list is likely to aid in foot clearance during gait. The effect of this pelvic list on the hips can be seen in the hip adduction angles, where intact side appears to be constantly in abduction.




2. We are currently estimating muscle force using Inverse Dynamics (ID). ID determines the generalized forces (e.g., net forces and torques) from an observed set of movements and its results can be used to infer how muscles are actuated to generate that motion. To determine these internal forces, the equations of motion for the system are solved with external forces (e.g., ground reaction forces) and accelerations given. This allows for the estimation of fibre length, fibre force, and tendon force throughout a set of movements.

3. These estimates of muscle loading will be collected across subjects and tasks. We hypothesise that subjects with lower muscle quality will have lower observed muscle loads.



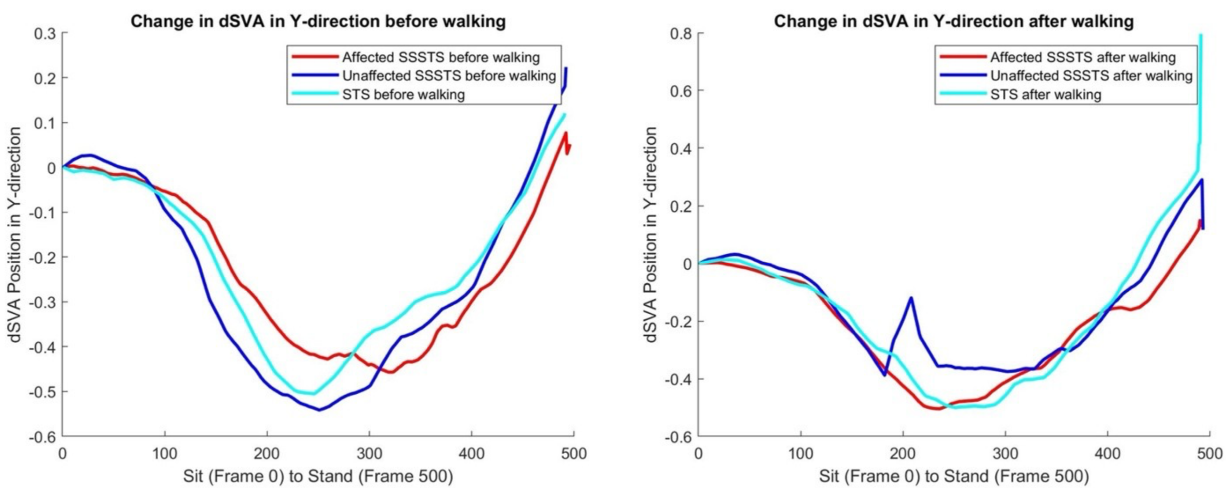




b. **Validating dynamics using prosthetic mounted force sensors**
In addition to the ground reaction force and motion simulations, a subset of subjects with osseointegration are performing these tasks while wearing a prosthetic mounted load cell. The iPECS load cell is located between the Axor failsafe and the proximal connector of the subject's prosthesis. The forces measured from this load cell can be used to validate the ID model. After the moments and forces in the model have been computed, they can be directly validated against the measurements from the iPECS sensor. If the forces

within the OpenSim simulation are validated, then these forces can also be applied to the FEM simulations. In the FEM simulation of the patient's femur and osseointegrated implant, the iPECS force sensor data would be used to directly introduce loading onto the implant and thus the patient's body. With the additional forces produced in OpenSim, the forces that occur around the patient's femur can also be added into the FEM simulations to replicate how the patient's muscles exert force on the femur and implant. By using a combination of iPECS sensor test results and results generated in OpenSim, a more realistic and accurate FEM simulation can be developed to quantify and predict the risk of bone fracture and implant failure in individuals with transfemoral osseointegrated prostheses.

c. **3D full-body kinematic motion assessment**

3D motion patterns of whole body time-series motion patterns will be compared for the Kinect staggered STS testing using statistical parametric mapping and statistical shape modeling. Three subjects performed the SSSTS on each leg as well as the STS directly before and after a bout of walking. The effect of the walking on the subjects performance during the sit to stand tasks was investigated. Prior to walking, the subjects performed similarly during the STS and the Unaffected SSSTS. However, when performing the SSSTS on the affected leg, there appeared to be a delay in the location of the absolute maximum dSVA, signifying that a larger portion of the movement was dedicated to leveraging out of the chair. After the bout of walking, there appeared to be an increase in absolute maximum dSVA during the affected SSSTS, likely a result of the fatigue from the walk. However, the opposite affect was observed for the unaffected SSSTS, while no change was observed for the STS. The bout of walking appears to exacerbate the difference in performance between the affected and unaffected leg. Fatigue may differentially effect the affected and unaffected limb. However, other factors, such as fear avoidance behaviors, may also play a role in these changes.




3) For hip muscle quality assessment in Aim 2:

a. [hip muscle quality measured via MRI Assessment] We have now processed 15 bilateral hip MRI scans through the combination of an automated segmentation model and manual segmentation of the Gluteus Medius (GMed), Gluteus Minimus (GMin), and Tensor Fasciae Latae (TFL). Water-only and fat-only IDEAl MR images are used for segmentation. The automated segmentation model is a machine learning algorithm that uses a 3D V-net algorithm—a 3-dimensional or “volume” neural network that predicts segmentation for the whole volume at once—by minimizing an objective function based on a dice coefficient. The dice coefficient is a statistic used to assess the similarity between two samples and is defined as the area of overlap between the predicted segmentation and the ground truth segmentation (provided by the fat-frac IDEAL MR image) divided by the total number of pixels in both images. This algorithm was trained and tested on 45 manual segmentations with a 65-20-15% train, validation, test split. Validation on a hip OA/healthy cohort produced the following dice coefficients (a value close to 1 is desirable): GMed = 0.93, GMin = 0.86, TFL = 0.89. Due to interference in particular slices and other image discrepencies some slices were manually segmented at the discretion of the researcher.

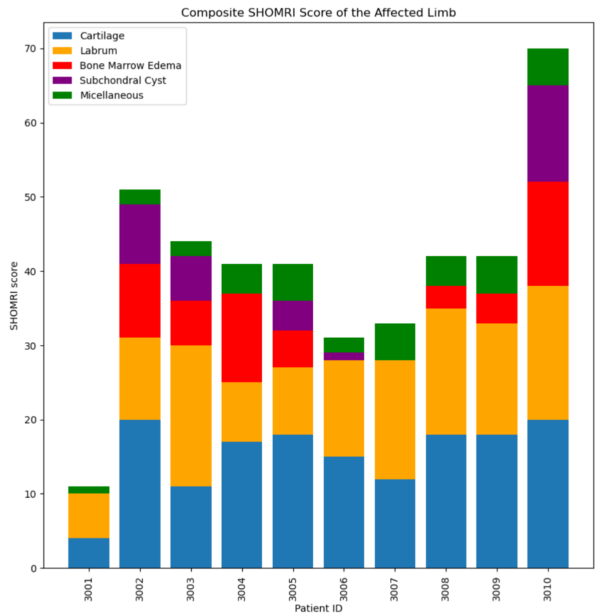
b. After segmentation, the images were prepared for fat fraction calculations. In order to account for spotty and incomplete results, the segmentations were manually adjusted and updated in Matlab. Masks of the segmentations were then applied to the DICOM volumes and voxels within the mask boundary and were classified as either fat or water. For each muscle a weighted, or volumetric, fat fraction was calculated using software in IPP in MatLab. The data for the osseointegrated patients shows a significant increase in cross-sectional-area from the affected to unaffected side in the Gluteus Medius and Gluteus Minimus ($p<0.04$). There were no significant differences between the affected and unaffected side in the conventional prosthetic patient, the THA patients, or the controls; however, it is interesting to note that the conventional prosthetic patient and osseointegrated patients followed a similar trend with an increase in fat in the affected side, and a decrease in muscular CSA. In contrast, while THA patients did have an increase in fat on their affected side, they did not have a decrease in cross section area. To assess the nature of muscle loss, we calculated the fat and lean muscle CSA in each slice of each patient. Fat CSA was calculated by multiplying the fat fraction by the total muscle CSA, and lean muscle area was calculated by subtracting the fat CSA from the total muscle CSA. We then looked at the percent change in fat CSA and lean muscle CSA between the affected and unaffected legs for the osseointegrated patients and between each leg of the controls. We found that on average, the fat CSA changed at a faster rate than the lean muscle CSA for all three muscles between the affected and unaffected leg of the osseointegrated patients, and that there was little to no difference in the rate of change bilaterally in any of the muscles for the controls (see blue box in table below). This information leads to the conclusion that while the total muscle CSA is decreasing, the fat CSA is also increasing such that there is proportionally more fat in the affected leg than the unaffected leg of osseointegrated patients. Next steps will include doing this same analysis on the THA patients, as well as testing the statistical significance of our findings.

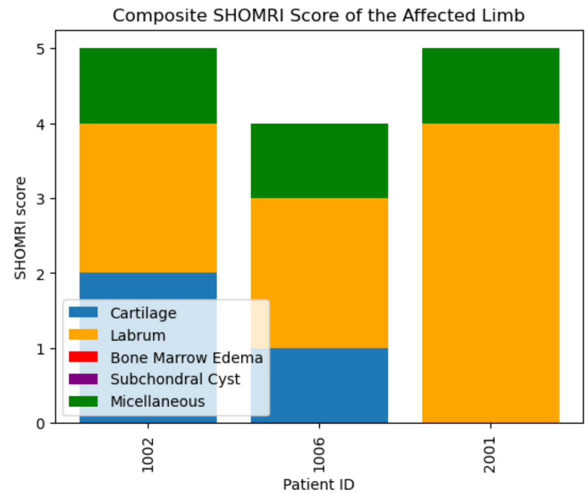
| Patient | Muscle | Fat % Change | Lean Muscle % Change |
|---|---|---|---|
| 1002 | Gmed | -0.41 | 0.004 |
| | Gmin | -0.49 | 0.005 |
| | TFL | 1.37 | -0.014 |
| 2002 | Gmed | 5.49 | -0.055 |
| | Gmin | 5.44 | -0.054 |
| | TFL | 13.89 | -0.139 |
| 2003 | Gmed | 9.57 | -0.096 |
| | Gmin | 11.99 | -0.120 |
| | TFL | NAN | NAN |
| Controls | Gmed | -0.29 | 0.003 |
| | Gmin | -0.30 | 0.003 |
| | TFL | -0.79 | 0.008 |

comparison

| Gmed Fat Average | Gmin Fat Average | TFL Fat Average |
|---|---|---|
| 4.88 | 5.65 | 7.63 |
| | Controls | |
| -0.29 | -0.30 | -0.79 |
| | | |
| **Gmed Muscle Average** | **Gmin Muscle Average** | **TFL Muscle Average** |
| -0.049 | -0.056 | -0.0765 |
| | Controls | |
| 0.003 | 0.003 | 0.008 |

c. In addition to fat infiltration analysis, we also scored hip osteoarthritis with MRI (SHOMRI) using a whole joint osteoarthritis evaluation. This method was tested and validated on 98 subjects and “demonstrated moderate to excellent reproducibility and significant correlation with radiographic gradings and clinical parameters” [Lee, et.al 2015]. For the purposes of this study, a radiologist used the SHOMRI method to assess the femoral and acetabular regions of THA and osseointegrated patients for cartilage health, bone marrow edema patterns, subchondral cyst formation, and labrum health. The information gathered from scoring will be assessed in tandem with muscle quality and kinematic motion data further enhance our understanding of subject hip health. The figures above show the weighting of the composite SHOMRI scores for THA patients (left) and osseointegrated patients (right). A maximum score of 96 shows severe osteoarthritis. Next steps will be to compare muscle quality,  kinematic data, and SHOMRI scoring to better understand the way one measurement affects the others.



**What opportunities for training and professional development has the project provided?**

PhD Students: Development of biomechanical tasks for this study have been provided by Karim Khattab, a graduate student in the Joint Bioengineering PhD program between UCSF and UC Berkeley. This project has advanced his training through mentorship from myself and Dr. Matthew (study Co-Investigator) to further develop the sit-to-stand and staggered sit-to-stand biomechanical assessment for this study. He will also be helping develop the gait assessment.

Fellows: UCSF radiology fellow, Zehra Akkaya, helped us with scoring the hip joints for OA severity and she will be included as a co-author.

Medical students: UCSF first-year medical student, Adrian Valderrama, attained a 2021 summer research fellowship to work on the MRI analysis component on this study.

Masters students: Dr. Matthew is working with a team of mechanical engineering masters students from UC Berkeley to develop relevant biomechanical modeling for the proposed study.

**How were the results disseminated to communities of interest?**

Nothing to report.

**What do you plan to do during the next reporting period to accomplish the goals?**

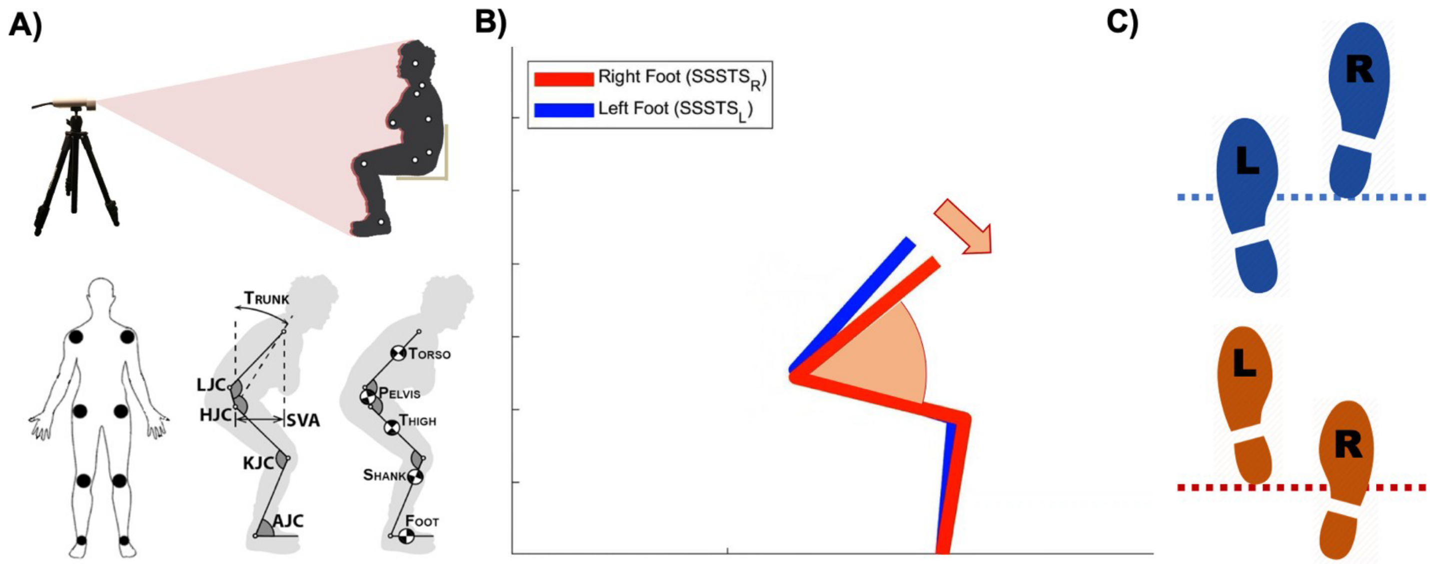
By the end of Y4Q1, our goals are: 1) recruit 1 more transfemoral osseointegrated patient, 2) submit first abstract (to Orthopaedic Research Society) on this work, and 3) begin working on final analyses

Currently, we do not anticipate any additional delays due to COVID and currently there are no more restrictions on non-essential human subjects research.

## 4. IMPACT:

**What was the impact on the development of the principal discipline(s) of the project?**

Our growing work on developing the in-clinic biomechanical assessment for the staggered sit-to-stand has shown differential compensatory biomechanics that we are using to understand the effects of lower limb biomechanical dysfunction and pain on whole body biomechanical stability. We will be using this staggered sit-to-stand approach as a part of our biomechanical assessment within this grant, but we are also able to use it in the clinic with 3D depth mapping cameras to collect quick and non-invasive routine biomechanical data on our lower limb amputees. This will ultimately contribute more robust and quantitative outcomes for tracking patient function and recovery.




The figure above presents the staggered sit-to-stand biomechanical assessment. We use markerless 3D depth mapping to track joint positions of patients as they rise in and out of a seated position (Panel A, top). Then with limb length constraints and noise filtering algorithms we are able to estimate accurate patient-specific kinematics and dynamics during the maneuver (Panel A, bottom). For this test, we have the patients do separate trials with their feet staggered to require them to rely more on the posterior placed foot (Panel C). Doing this, we find distinct compensatory biomechanical strategies that correspond with loading on unaffected versus affected lower limbs (Panel B, Right side affected).

**What was the impact on other disciplines?**

Our study seeks to understand the effect of hip muscle health on biomechanical dysfunction in transfemoral amputees in order to understand risk if there is elevated risk for developing hip osteoarthritis or needing a future hip surgery. Therefore, there is a natural symbiosis between what we are developing as part of this study on hip health in transfemoral amputees and our non-amputee hip osteoarthritis and arthroplasty patients. This staggered sit-to-stand test is now also being used in the arthroplasty clinic at UCSF to amass a database of biomechanical data on subjects with advanced hip osteoarthritis in order for us to compare our transfemoral amputee data too in order to better understand how biomechanical behaviors in our amputees may be indicative of hip dysfunction. However, by integrating this tool into the hip clinic, we can use it to track changes pre- and post-op recovery of total hip replacement and ultimately use pre-operative biomechanical function to possibly predict risk for poor post-operative outcomes.

**What was the impact on technology transfer?**

Nothing to Report.

**What was the impact on society beyond science and technology?**

Nothing to Report.

## 5. CHANGES/PROBLEMS:

**Changes in approach and reasons for change**

Nothing to Report.

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

**COVID delays:** Currently, we do not anticipate any additional delays due to COVID and currently there are no more restrictions on non-essential human subjects research.

**MRI eligibility:** Our first three study subjects were all transfemoral osseointegration patients and two of which were not able to safely have hip MRIs due to unanticipated factors that can cause discomfort/heating, like 1) pre-existing shrapnel in the residual limb, and 2) existing hardware in the hip. These were the only two patients that we know of with factors that would impede their ability to have a hip MRI and fortunately, more osseointegration patients will become eligible for our study soon, enabling us to increase our sample size to have at least eight osseointegration patients with both MRI and biomechanical analysis.

**Changes that had a significant impact on expenditures**

Nothing to report.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to Report.

**Significant changes in use or care of human subjects**

Nothing to Report.

**Significant changes in use or care of vertebrate animals.**

N/A

**Significant changes in use of biohazards and/or select agents**

N/A

## 6. PRODUCTS:

**Publications, conference papers, and presentations**

i. **Journal publications.** Nothing to Report.

ii. **Books or other non-periodical, one-time publications.** Nothing to Report.

iii. **Other publications, conference papers, and presentations.** Nothing to Report.

**Website(s) or other Internet site(s)**

Nothing to Report.

**Technologies or techniques**

Nothing to Report.

**Inventions, patent applications, and/or licenses**

Nothing to Report.

**Other Products**

*Nothing to Report.*

**PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**What individuals have worked on the project?**

| | |
|---|---|
| Name: | Jeannie Bailey |
| Project Role: | Principal Investigator |
| Researcher Identifier (e.g. ORCID ID): | https://orcid.org/0000-0003-4618-7512 |
| Nearest person month worked: | 2 |
| Contribution to Project: | Dr. Bailey has worked to initiate the study with IRB approval, establish MRI protocols and have them in place for human subjects, and mentored Graduate Student Karim Khattab on developing Biomechanical Assessment. |
| Funding Support: | This award. |

| | |
|---|---|
| Name: | Robert Matthew |
| Project Role: | Co-Investigator |
| Researcher Identifier (e.g. ORCID ID): | https://orcid.org/0000-0002-8649-2506 |
| Nearest person month worked: | 2 |
| Contribution to Project: | Dr. Matthew has worked on developing analysis for the sit-to-stand testing and mentored Graduate Student Karim Khattab on developing Biomechanical Assessment. |
| Funding Support: | This award. |

| | |
|---|---|
| Name: | Richard O'Donnell |
| Project Role: | Co-Investigator |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 1 |
| Contribution to Project: | Dr. O'Donnell has helped with patient recruitment. |
| Funding Support: | This award. |

| | |
|---|---|
| Name: | Roland Krug |
| Project Role: | Co-Investigator |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 1 |
| Contribution to Project: | Dr. Krug has worked advanced imaging MRI sequences for this study. |
| Funding Support: | This award. |

| | |
|---|---|
| Name: | Karim Khattab |
| Project Role: | Graduate student |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 1 |
| Contribution to Project: | Dr. Khattab has worked on developing Biomechanical Assessment. |
| Funding Support: | Graduate fellowship |

| | |
|---|---|
| Name: | Adrian Valderrama |
| Project Role: | Medical student |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 1 |
| Contribution to Project: | Adrian is working on MRI analysis for this study. |
| Funding Support: | Research fellowship. |

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to Report.

**What other organizations were involved as partners?**

Nothing to Report.

**7. SPECIAL REPORTING REQUIREMENTS**

**COLLABORATIVE AWARDS:** Nothing to Report.

**QUAD CHARTS:** Updated milestone timeline projections.

**8. APPENDICES:** N/A