Statistical Analysis Plan (SAP)

New Tools for Assessing Fracture Risk

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1. Introduction

The goal of this study is to determine whether the OsteoProbe®, an inpact micro-indentation device, or bound water and pore fraction by MRI can discriminate between high-energy fractures of normal bone (trauma) and low-energy fractures (fragility) of osteoporotic bone. The current gold-standard for assessing fracture risk is the measurement of areal bone mineral density (aBMD) by dual energy X-ray absorptiometry (DXA). Yet, the age-related and diabetes-related increase in fracture risk is often independent of a person's aBMD. These findings stress the urgency in developing diagnostic tools that can improve fracture risk prediction so that patients can be treated with the appropriate anti-fracture therapies.

By affirming the ability of the OsteoProbe® to discriminate a fragility fracture from high-energy (trauma) fracture, the proposed study will provide justification for large prospective studies that i) evaluate the ability of these techniques to predict fracture risk of the hip and spine, ii) assess whether these techniques are informative on how drug therapy affects bone, and iii) whether intra-operative RPI is useful to surgical guidance.

2. Study design

Men and women (>18 y.o.) undergoing surgery to fix a distal radius, Colles' type fracture will be recruited into the study. Exclusion criteria will include known risk factors of pathological fractures (e.g., bone metastasis) and treatment for osteoporosis within the past 5 years (e.g., bisphosphonate). In addition to standard-of-care, the orthopaedic surgeon will indent the cortex between the one-third distal radius (10 sites separated by 2 mm) and the ultradistal (UD) site with the OsteoProbe prior to stabilizing the fracture with a volar plate. Within a few weeks of surgery, the patient's hips, spine, and contra-lateral radius will be imaged by DXA to determine aBMD following standard protocols at the Vanderbilt Diet Body Composition, and Human Metabolism CORE. Patients will be stratified into two groups: high-energy fracture (e.g., motor vehicle crash) of *normal bone* and low-energy fracture (e.g., fall from a chair or standing height) of *osteoporotic bone*. We expect a lower BMSi for the fragility fracture than for the high-energy fracture group will be significant when including aBMD or age as covariates.

On the same day that the patients in Aim 1 receive a DXA scan, they may also have their contralateral arm (distal one-third) imaged by our unique UTE-MRI technique (Philips Achieva 3T scanner) using wrist coil at VUIIS. By including reference markers in the scan, the average concentration of bound water and pore water (mol ^{1}H per bone volume) will be quantified for a 14 mm axial segment (0.5 mm in-plane resolution). We will also image age-matched and sex-matched individuals without a history of fractures to the operative fragility fracture group. We expect the fragility fracture patients to have significantly less bound water and more pore water than high-energy fracture patients and non-fracture patients, and this difference will be significant after adjusting for aBMD or age.

2.1. Sample Size Calculation

Based on the variance from our cadaver studies and expected mean BMSi for 'normal' bone as measured by Farr et al. (J Bone Miner Res. 2014), a sample size of 15 per group will provide 87% power to detect a 11.2% difference between the 2 cases at an α of 0.05.

3. Aims and Objectives

AIM 1: DETERMINE WHETHER INDENTATION RESISTANCE IS DIFFERENT BETWEEN PATIENTS WITH FRAGILITY FRACTURES AND THOSE WITH HIGH-ENERGY FRACTURES.

Hypothesis: Local indentation resistance (BMSi) of the distal one-third radius is lower for patients with a fragility wrist fracture than healthy patients with a traumatic wrist fracture after adjusting for age or aBMD.

AIM 2: DETERMINE WHETHER BOUND WATER AND PORE WATER ARE DIFFERENT BETWEEN PATIENTS WITH FRAGILITY FRACTURES AND SUBJECTS WITHOUT BONE DISEASE.

Hypothesis: Bulk bound and pore water of the distal one-third radius will be lower and higher, respectively, for patients with fragility wrist fractures than healthy patients with or without a traumatic wrist fracture.

4. Outcomes

This section will present the outcomes investigated to answer the study aims.

4.1. Primary Outcome

Osteoprobe Measurements- Bone Material Strength index (BMSi)

MRI Scan Measurements- Bound Water Fraction

MRI Scan Measurements- Pore Water Fraction

DXA Scan Measurements- Bone Mineral Density

DXA Scan Measurements- Bone Mineral Content

DXA Scan Measurements- T-Score

4.2. Secondary Outcome

Patient-reported Measurements

DASH (Disabilities of the Arm, Shoulder, and Hand) Score

PRWE (Patient-rated wrist evaluation) Score

4.3. Safety outcomes

Adverse events and study complications are documented at each study time point.

5. Populations and subgroups to be analyzed

5.1. Populations

Primary population- This study consists of three study arms.

Study arm 1- Adult patients who have elected to undergo volar plate fixation of a distal radius a fracture due to a high-energy or low-energy event.

Study arm 2- Adult healthy volunteers who are age-matched and sex-matched individuals without a history of fractures to the operative fragility fracture group.

Study arm 3- Adult patients who require nonoperative treatment of their distal radius fracture due to a high-energy or low-energy event.

5.2. Subgroups

High energy versus low energy fractures

Participants in study arm 1, those with a distal radius fracture that required volar plate fixation, will be stratified into two groups: high-energy fracture of normal bone and low-energy fracture of osteoporotic bone.

Low energy fractures vs. non-fracture control

Participants in study arm 2, those without a fracture or osteoporosis, will be the control group to the low-energy fracture subjects in study arm 1 (operative) and 3 (non-operative)

6. Analysis

Statistical comparisons will be performed using two-sided tests at the 5% significance level. Mann-Whitney test will assess whether differences in properties between groups are statistically significant. Next, general linear models (GLMs) will be used to determine whether the case explains each property after adjusting for aBMD (or T-score) or age. Using a robust analysis with GLMs, the data will be bootstrapped with 500 replicates.

6.1. Primary outcome

The primary analysis will compare:

- BMSi of the distal one-third radius in patients with a fragility wrist fracture to healthy patients with a traumatic wrist fracture after adjusting for age or aBMD.
- Bulk bound and pore water of the distal one-third radius in patients with a fragility wrist fracture (low-energy) to healthy patients without a traumatic wrist fracture

6.2. Secondary outcome

The secondary analysis will compare the mean change in patient reported outcome measure scores from baseline (preoperative visit) to 3 week, 6 week and 12 week postoperative time points.