Research Protocol

A Prospective Study of Human Bone Adaptation Using a Novel in Vivo Loading Model

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This Human Subjects Research meets the definition of 'Clinical Research'.

Introduction:

Aim 1 and Aim 2 describe two clinical research studies that will each recruit 20 women per group age 21 to 40. Therefore, a total of 100 subjects in total will participate. The subject characteristics, basic intervention description, data collection, risks, and potential benefits are the same for both Aims. The only distinction between the two studies is the variable that is being manipulated; strain magnitude for Aim 1 and strain rate for Aim 2. The following document refers to the studies in both Aims.

Protection of Human Subjects

1. Risks to the Subjects

a. Human Subjects Involvement and Characteristics

One hundred healthy women age 21-40 will be recruited to participate in two clinical research experiments. Inclusion/exclusion criteria are summarized below:

***Inclusion criteria*: Age 21-40, free of endocrinopathies, distal radius BMD t-score -2.5 to +1, no known thyroid, vitamin D or calcium abnormalities, normal body weight (BMI 18 to 25), 9-14 menstrual cycles per year.**

***Exclusion criteria*: Fracture within 5 years, arthritis in wrist, diabetes, severe disabling conditions, cancer within 5 years, metabolic bone disease, use of androgen, estrogen, progesterone, calcitonin, SERMs, PTH, GnRH and analogs within 6 months, corticosteroids within 3 months, bisphosphonates or fluoride within 3 years, cardiovascular or pulmonary disease, uncontrolled hypertension, daily tobacco use, alcohol> 4 drinks/day, pregnancy or lactation within 2 years, or plans to become pregnant or donate eggs in the next year. Individuals using hormone-based contraceptives are not excluded, with the exception of those having used depot medroxyprogesterone acetate within the past 6 months. Individuals who participate more than twice per month in sports that load the upper extremities, such as gymnastics, tennis or softball, will be excluded, as will those with low calcium intake (i.e. those avoiding dairy products unless taking calcium supplements).**

Rationale for this population:

Although an older (potentially osteoporotic) subject population is of clinical relevance, the purpose of the present study is to show and define the effect of various aspects of mechanical loading signal. Our pilot data demonstrate that the proposed intervention is osteogenic in the proposed population, which will allow us to further examine these signal characteristics in detail. Ultimately, it is our view that mechanical loading interventions will be *most* effective as a preventive tool to improve peak bone mass and bone mechanical properties in adolescents and younger adults. It has been demonstrated that high levels of physical activity, especially during growth, cause improvements to bone mass and structure that persist throughout the lifespan (Barnekow-Bergkvist, 2006). The notion of maximizing peak bone mass to protect against age-associated declines in bone strength is accepted as logical and reasonable. Given the short-term benefits of the proposed loading regime that we observed in our pilot data, the subjects who participate in this longer-term research study are likely to experience clinically relevant increases in distal radius peak bone mass and mechanical properties, potentially reducing lifetime fracture risk at this site.

Women attain peak BMC and BMD at the ultra-distal radius at age 23 and 19 respectively, and attain 94% and 98% of peak BMC and BMD by age 16 (Henry, 2004). These measures remain at peak until age 40. Changes measured during the proposed study period in a population of 21-40 year old women can, therefore, be attributed to the mechanical loading intervention.

Here we focus on women only. Given the high rate of osteoporosis that this population develops later in life, this seems a well intentioned priority. We intentionally exclude women who were recently pregnant, are lactating, or who have plans to become pregnant. Pregnancy and lactation represent

altered physiologic states that are associated with increased bone turnover. We also exclude children because they have not yet reached skeletal maturity.

Recruitment:

Volunteers will be recruited from the communities surrounding Worcester Polytechnic Institute (WPI) including announcements made electronically and in person by members of the research team. Flyers and pamphlets explaining the study will be placed in the community, and, with permission, in the waiting room of the Family Practice clinic at the University of Massachusetts Medical Center. We will work with the institutional review board at WPI to ensure that all subject recruitment materials are compliant.

Screening:

All subjects will be verbally screened for inclusion/exclusion criteria by a member of the research team prior to being invited for a screening visit. During the screening visit, the subject's height and weight will be recorded. Subjects will receive a DXA scan of their nondominant radius and only those with BMD that falls within the specified range for inclusion will participate. Subjects will then visit the Quest Diagnostics Collection Center. There, six ml blood will be drawn via standard veinpuncture and sent to a local diagnostic laboratory (Quest Diagnostics) for a full metabolic profile including measurement of TSH, estridiol levels and Vitamin D concentration (total and 25,OH D_2 and D_3). This data will be interpreted by Drs. Schnitzer and Troy. Potential subjects who have abnormal data and do not qualify for participation will be contacted by Dr. Schnitzer, given a copy of their laboratory results, and advised to consult their primary care physician. Dr. Schnitzer will provide each of these individuals with his own clinical interpretation of the data, so that they understand the importance of their results.

All potential subjects who qualify to participate based on their screening will be invited to participate in the study. A signature of the informed consent document is considered a subject's written affirmation that she fits the inclusion/exclusion criteria.

Group Assignment:

For each Aim, eligible subjects will be randomized to one of two loading groups: a low, or a high group (20 subjects each) by having subjects draw a sealed envelope containing the group assignment. An additional 20 subjects will be randomized to a control (observation only) group. It is not possible to blind subjects or all team members to group assignment due to the nature of the experiment (team members cannot be blinded because group assignments must be known to assign target forces). However, all data will be blinded for analysis.

- **For Aim 1 the low and high groups refer to low and high strain magnitude. Subjects in each of these groups will be assigned a target force based on their individual anatomy and their group assignment. The low and high strain groups will be assigned strain magnitudes of 1800 micro-strain ($\mu\varepsilon$) and 3600 $\mu\varepsilon$ respectively. The forces required to produce these strains typically range from 300 to 500 N (0.5 to 0.8 body-weights).**

- **For Aim 2 the low and high groups refer to low and high strain rate. Subjects in each of these groups will be assigned a target force based on their individual anatomy, and will be given one of two instruction sets that will assist subjects in producing slower or more rapid forces. The slow strain rate group will be given a target loading rate of 4500 $\mu\varepsilon$/s (i.e., 3600 $\mu\varepsilon$ achieved in 0.8 seconds. The impact strain rate group will be given a target loading rate of 36,000 $\mu\varepsilon$/s (i.e., 3600 $\mu\varepsilon$ achieved in 0.1 seconds). The slow group will be instructed, "Each time you hear a beep, lean on your hand to reach the target force, loading and unloading your hand as slowly and evenly as possible." In pilot subjects, this resulted in a load application time of 0.8 seconds. The impact group will be instructed to "Stand approximately 15 inches away from the device (which is placed on a hip-high table). When you hear a beep, fall forward until your hand contacts the load cell. You may need to adjust how close you stand to achieve your target force." In pilot subjects this resulted in a load application time of 0.1 seconds. Subjects in the control group will continue their regular physical activity.**

Rationale for Doses:

- **For Aim 1, to determine the target strain range, pilot subjects were classified as high and low responders (five and three subjects, respectively, based on observed 14 week changes in ultradistal BMC of +2.57% and +0.51%). On average the high responders' peak Von Mises equivalent strains within the ultradistal volume were 3430±536 με, whereas the low responders' were 2125±432 με. Based on these results, we conclude strains below 1800 με are unlikely to elicit a response, whereas we observed that strains above 3600 με required forces in excess of 450 N for the average subject. Many women have difficulty applying this magnitude. Thus, targets of 1800 and 3600 με were identified for this experiment.**

- **For Aim 2, the target strain magnitude, 3600 με, represents the largest strain magnitude that is achievable voluntarily by most female subjects. In our pilot subjects, this required a target force of 445±80 N. Using the largest reasonable strain value maximizes the possible strain rate that is achieved with the impact loading group and maximizes the possibility that the loading elicits an osteogenic response. The strain rates that are assigned, 4500 με and 36,000 με, respectively, are a function of the load application time generated with each of the two instruction sets. *The range of strain magnitudes produced using "slow" versus "impact" instruction sets represent nearly the entire range that can be voluntarily produced safely and consistently by subjects*.**

- **In both aims, subjects will apply 100 cycles of loading per day, 4 days per week, for 12 months. In our pilot subjects, this number of cycles per week was well tolerated by subjects and was osteogenic.**

b. Sources of Materials

All research data will be obtained from the subjects specifically for research purposes.

- **QCT data is uploaded to a secure cloud-based website (www.LifeImage.com) for transfer to the laboratory. Per hospital procedure, all CT scans are read by a radiologist to ensure that no abnormalities are detected. Should the scan reveal abnormal pathology, the subject will be contacted directly by the radiologist. The CT scan is documented in each subject's medical record as a research CT scan.**
- **DXA data, used for screening purposes, is acquired at the University of Massachusetts Medical Center and results are uploaded to LifeImage for transfer to the laboratory.**
- **High-resolution CT data (HR-pQCT; XtremeCT, Scanco, Switzerland), is acquired in our Laboratory at Worcester Polytechnic Institute using the manufacturer's estabolished procedures. All scans are performed by a licensed Clinical Bone Densitometry Technician (CBDT; Karen L. Troy). Scans are saved in de-identified form.**
- **Blood will be acquired from subjects using standard veinpuncture. A trained nurse or phlebotomist will draw the blood, which will be sent to a local diagnostic laboratory for processing. This is done for screening purposes only and does not go into a subject's medical record. All specimens are fully anonymized.**
- **Load cell data will be acquired from the data logging devices that each subject will be given. The data consist of voltage versus time recordings and are not considered medical information.**

All research team members will have access to the data collected. In addition, QCT and DXA data is part of the subject's medical record and can be accessed by the radiologist who will read the CT. Blood specimens will be accessed by Quest Diagnostic Laboratory and all results will be sent directly to the Principal Investigator and Co-investigator Schnitzer for interpretation.

When a potential subject arrives for screening she will be assigned a study ID number, which will be used to track her blood and HR-pQCT data. Should that subject enroll in the study, that study ID will be used for all additional data collection. The only exception to this is QCT and DXA data, which are acquired on the hospital scanners. Per hospital procedures, subject names will be associated with their data. However, data will be anonymized and relabeled with the subject study ID as soon as it is taken to our laboratory.

c. Potential Risks

The risks of this study are related to the radiation dose that subjects will receive during DXA and CT scans, and due to the direct loading they will apply to their wrist. All subjects will take a urine pregnancy test prior to receiving any DXA or CT scan. All DXA and CT scans will be prescribed by a physician.

i. Radiation Dose: Each DXA scan exposes subjects to a total radiation dose of 0.05 mrem and subjects will receive one DXA scan each during screening. CT scans will result in an estimated radiation dose to subjects of 9 mrem per scan. HR-pQCT scans result in an effective radiation dose of 0.3 mrem per scan.

Subjects will receive 20.45 mrem (1 DXA plus 1 CT scan per arm x 2 arm x 9 mrem/scan plus 4 HR-pQCT scans/arm x 0.3 mrem/scan) over the first 12 month period, and 19.8 mrem (1 CT scan per arm x 2 arms + 3 HR-pQCT scans/arm x 2 arms) over the second 12 month period is expected.

ii. Mechanical Loading: Direct loading to the distal radius may cause some discomfort to subjects.

The alternative is to not participate in the research study.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

Subjects will be recruited through physician referrals and by use of flyers, brochures, and word of mouth. Subjects will contact the Biomechanics Laboratory in response to either being directly asked to participate, or to seeing information about the study. If a subject appears to meet the study criteria, a letter of invitation will be sent to the potential subject and an appointment will be scheduled for them to speak with a member of the investigative team.

We believe that informed consent is a process that begins at the letter of invitation and/or when subjects inquire about the study and does not end until they have completed the study. When the initial personal contact is made with subjects, usually by phone, an appointment is made to talk to the potential subject and explain the study in its entirety. Research staff will explain the purpose of the study, study procedures, benefits, risks, confidentiality and privacy, and the subject's rights. Since this study involves a substantial long-term time commitment on the part of the subject, time commitment is emphasized during the consenting process. The written consent is reviewed in detail and is used as a guide for the person obtaining the consent. The subjects are encouraged to ask questions throughout this process. The informed consent procedure generally takes 30-60 minutes to complete. Subjects are encouraged to take the consent home and review it with their family and/or their doctor before signing. Some subjects insist on signing the consent the same day that the study is explained. If this occurs, the subject is given a copy of the consent to bring home and informed again that they are free to withdraw at anytime.

Subjects will be paid for their participation in the study. The payment is intended to defray travel costs and to compensate subjects for their time. The amount of reimbursement is not excessive and will not be emphasized during the recruitment process.

Karen Troy, PhD, or another qualified lab member will obtain informed consent from all subjects. All investigators are experienced in administering informed consent and have dealt directly with the Institutional Review Board in the context of obtaining approval for studies. All personnel involved in research have completed IRB human subjects training.

b. Protection Against Risk

Radiation Dose: The maximum amount of radiation that a subject will be exposed to during a 12-month period is 21 mrem. For comparison, the average annual radiation exposure from natural sources is about 310 mrem. The Nuclear Regulatory Commission recommends that radiation exposure originating from medical/diagnostic sources be limited to 100 mrem annually if possible, and our study falls within this limit. Studies of radiation dosimetry have estimated that the biological impact of radiation applied to extremities such as the forearm is substantially less than radiation applied to the brain or abdominal organs. As additional protection, all subjects will be covered with a lead apron

during DXA and CT scans, and only the scanned body part will be exposed. All subjects will be required to have a negative pregnancy test prior to DXA or CT scans.

The HR-pQCT is located within the Musculoskeletal Biomechanics Laboratory, and access is limited to members of the lab and experimental participants only. All doors are locked and a licensed bone densitometrist (Karen Troy) is responsible for all data collection. A physician will order all DXA and CT data acquisition. The CT is housed in the University of Massachusetts Medical Center and is operated by a licensed radiology technician.

Mechanical Loading: The maximal self-imposed strain that will be applied to a subject's wrist is 3600 με. This is approximately the magnitude of strain achieved during a push-up. The force required to produce this strain ranges from 300 to 450 N for most subjects (i.e. 0.5 to 0.8 times body weight), and is dependent upon each individual's bone geometry and strength. Loading will be accomplished by asking subjects to lean from a standing position onto their hand, which will be placed on a load cell. During the first four weeks subjects will gradually increase the amount of force with which their wrist is loaded until they reach their subject-specific target load. Subjects will be instructed not to load their wrists to a painful degree; if a subject's wrist becomes painful during the loading protocol she will be instructed to stop and take a rest until she feels ready to continue. If a subject is unable to load her wrist with a force of at least 300 N (because of pain or lack of strength) during the initial screening, she will be considered ineligible to participate in the study. Subjects at risk for mechanical damage through the low-magnitude loads in the present study (such as those with osteoporosis) will be excluded from participation. A previously completed pilot study indicates that a forces of 300 to 500 N applied voluntarily to the wrist is achievable and well-tolerated by healthy adult women.

Confidentiality: All research data will be coded for data entry so that a patient's identity cannot be determined (e.g., young001, young002). CT data will be anonymized. There will be no computerized link to a research subject's identity. All computer files will be password protected and available only to those involved with the research. There will be a log book maintained by Dr. Troy linking the computerized identifier with the subject's name. This log book will be kept in a locked file cabinet in the research offices that are also kept locked at all times. Subject study files will be maintained in locked research offices at all times. After all of the data are analyzed the research data will be stripped of identifiers and stored indefinitely. These procedures will be explained to subjects at the time of completing the informed consent.

3. Potential Benefits of the Proposed Research to the Subjects and Others

The risks to subjects are low when compared to the potential benefits of participation. All subjects will receive information about factors affecting their initial bone health such as Vitamin D levels and bone mineral density. If potential subjects have abnormal concentrations of Vitamin D, for example, they will be advised to contact their primary care physician to develop a plan to increase Vitamin D intake. Due to a high rate of low blood Vitamin D levels observed, the research team has developed a standard reporting form to return laboratory results to all subjects who are screened, and to provide contextual information from the NIH and CDC about recommended daily Vitamin D intake. In this way all potential subjects will have increased awareness of issues related to bone health. All subjects assigned to a loading group have the potential to increase their bone quality. In addition to the probable increase in strength of the loaded arm, subjects may have a decreased risk of fracture in that arm for a prolonged period of time after completing the intervention. Additionally, all subjects will be aware of the influence that loading has on their bone health and may be motivated to continue a loading/exercise program on their own after the study is complete.

4. Importance of the Knowledge to be Gained

The contribution of the proposed research is expected to be a detailed understanding of how human bone structure and strength are modified in response to changes in mechanical loading environment. This contribution is significant because it is the first step in a continuum of research that is expected to lead to the development and evaluation of optimized exercise strategies that improve bone strength and lead to long-term reductions in the incidence of fractures. Combined with musculoskeletal modeling, the knowledge gained here could be used to prospectively estimate the expected changes in bone structure and strength resulting from any variety of exercise interventions.

Furthermore, future work that involves populations with known differences in bone metabolism, such as those on anabolic or antiresorptive therapy, lactating women, adolescents, or those with recent healing fractures, would allow us to elucidate the degree to which adaptation is altered by these differences in bone metabolism. Our experimental approach involves upper extremity loading, which directly improves the bone mass and structure of the distal radius. This may provide research subjects with long-term skeletal health benefits at the distal radius, and this approach may serve as a basis for a new bone strengthening regime that targets this common fracture site.

5. Data and Safety Monitoring Plan

This study is considered to be over all low risk. The experimental treatment, mechanical loading, is voluntary and has been well tolerated by subjects in the past. The data collection methods involve some risk in that there is radiation exposure. Subjects' decision making capabilities are not expected to be affected by their participation in this study.

The Principal Investigator, Dr. Karen Troy, and Co-investigator, Dr. Thomas Schnitzer, will monitor data and safety. Each month Drs. Troy and Schnitzer will review the available data on subject compliance, data collections, drop outs, and any reported adverse events. Observations and comments from subjects will also be noted. Special attention will be paid to drop outs and the reason for drop outs, since this may be an early indicator that the mechanical loading is not well tolerated by subjects.

The magnitude of mechanical loading prescribed to each subject will be decreased if the subject is having difficulty achieving the magnitude or if she experiences pain during or after loading. If more than two subjects experience pain the dose of mechanical loading will be decreased for all subjects. In no case will the mechanical loading dose be increased beyond the planned 100 cycles per day, 4 days per week and 450 N.

Quality control and data completeness will be assured by Dr. Troy with assistance from the postdoctoral research fellow. All data will be collected within our laboratory except for DXA and CT scans, which will be acquired at the University of Massachusetts Medical Center. A team member will personally interface with the radiology technicians at the medical center to ensure that a standard protocol is being used to scan all subjects. Additionally, a team member will personally accompany subjects to the CT scanner on a regular basis and will be present in the technician's room during select scans to ensure quality.

Any temporary or permanent suspension of the study by any supervisory body, including NIH, the IRB, or the Principal Investigator, will result in the prompt notification of all relevant institutions. Prior to commencing this research a pre-study meeting will take place and will be documented to ensure that investigators, research assistants, and other essential personnel are aware of the protocol requirements and methods of data collection.