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CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY

Title:
The Impact of Osteoporosis Medications on Muscle Health in Older Adults

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Key Information

General Information	You are being asked to participate in a research study. Research studies include only people who choose to take part. The study team members will explain the study to you and will answer any questions you might have. You should take your time to make your decision. This study is about osteosarcopenia, which is the medical term for losing bone and muscle mass as we age.
Purpose and activities	The purpose of this study is to understand the effect of medications that are used to treat osteoporosis (porous bone) on muscle health. Research has shown bone and muscle are tightly connected and those who have healthier muscles have healthier bones. Muscle health also is important to activities of daily living and preventing falls. In this study we will examine the impact of medications that are used to treat osteoporosis on muscle mass (bulk), strength and function and will also assess correlation of muscle health with bone health. We will examine bone density (the amount of bone mineral in your bone tissue), bone quality and lean muscle mass by DXA scan, which is a whole-body x-ray that can measure bone and muscle mass (DXA stands for “dual-energy X-ray absorptiometry”). Other methods to measure lean muscle mass are the D3-creatine method and the muscle ultrasound. In D3-creatine method we use a substance called creatine. Creatine is found naturally in muscle cells. With muscle ultrasound we measure the thickness and surface area of your thigh muscles. We will also examine your muscle strength with a device called dynamometer by asking you to squeeze the dynamometer. We will check your muscle function by assessing your walking.
Duration & Visits	If you are eligible to take part in this research study, it will involve 4 study visits over the next 12 months (screening, baseline, 6 months and 12 month).

Overview of Procedures	• You will complete questionnaires, answer questions about your medical history and report falls and fractures. • You will receive either denosumab or zoledronic acid for management of your osteoporosis at baseline. You will also receive the placebo form of the other medication at the baseline. Denosumab is a subcutaneous injection and Zoledronic acid is an IV infusion. • In months 6, you will receive denosumab or placebo. • In months 12 you will receive zoledronic acid infusion. We will test your grip strength, balance and walking at the baseline and 12 months. • You will also have 2 DXA scans at the baseline and 12 months. The DXA machine has a table that you will lie on, where two X-ray beams will be aimed at your whole body to obtain images. • You will have ultrasound imaging to take pictures of your thigh muscles and measure its thickness and surface area at the baseline and 12 months. • We will ask you to swallow a capsule of a very small dose of D3-creatine and collect fasting urine samples at the start of the study and again 12 months later.
Risks	There are risks related to being in the study • Risk of the study drug • Minimal radiation exposure with DXA scans Less likely risks: • Pain, discomfort while doing the ultrasound • Skin reaction to the ultrasound gel • Difficulty with swallowing D3-creatine capsule There is more on risks on page 7-11.
Benefits	You will benefit by learning the mineral content and quality of your bones and how much lean muscle mass you have in your body from your DEXA scan, ultrasound, and the D3-creatine. You will also learn about your muscle strength and function and impact of osteoporosis management on your both bone and muscle health.

Who is being asked to take part in this research study?

You are being asked to participate in this study because you are:

1. Age 65 or older
2. Have been diagnosed with osteoporosis OR with osteopenia (low bone mass) and at high risk for fractures.

Approximately 40 females will be eligible to take part in the research study. Participants will be randomly assigned (by chance, a 50-50 chance such as with flipping a coin) to either Denosumab 60 mg sc or Zoledronic Acid 5mg IV which are both FDA approved drugs for treatment of osteoporosis. Of the 40 participants, 20 will receive the denosumab and 20 will receive the zoledronic acid. All participants will receive zoledronic acid at 12 months. All participants will receive calcium and vitamin D supplements.

What procedures will be done for research purposes?

If you decide to take part in this research study, the study visits will be done at the University of Pittsburgh Pepper SMART Center/Osteoporosis Prevention and Treatment Center located in Oakland, where you will go through some procedures that are not part of your standard medical care. Following obtain of your consent, this research study **will involve 3 study visits over the next 12 months (baseline, 6 month and 12 month).** During the baseline and month 12 visits we will give you questionnaires to document your calcium/vitamin D intake, medical and falls history. We will **obtain your written informed consent** before research study procedures are done.

Screening

This visit will take approximately ½ hours of your time and involve the following procedures.

1. Reviewing the informed consent form and procedures for the study
2. You will be provided with a 30 mg D3-creatine capsule and urine collection kit. This will be taken by mouth 2-4 days before the next visit. The capsule can be taken at any time of the day, however it should not be less than 48 hours (2 days) or over 96 hours (4 days) prior to the time you will present for your visit and provide an 8 hour fasting urine sample. Note that creatine is made by your body but can

also be taken as a dietary supplement. In this study, the creatine has been “deuterated” (that is what the D stands for in “D3-creatine”). This means there is a slight change to the chemical so that it can be traced in your urine. The risks are the same as the regular creatine. We may also mail you the D3-creatine capsule and the urine collection kit with their instruction.

Baseline Visit

This visit will take a total of approximately 1 ½ hours of your time and will involve the following procedures:

1. **Brief history** taking.
2. You will be asked about changes in your health since the screening visit and if you have had any broken bones or falls since then.
3. We will **test your grip strength, balance and walking.** You may be asked to do things like get up from a chair or walk down a hallway.
4. **Ultrasound**. Ultrasound imaging for this study will obtain images used to measure the thickness and surface area of your thigh muscles. For the ultrasound procedure, you will have ultrasound gel applied to the top of your thigh. You will be asked to straighten your leg for up to 10 minutes while the ultrasound probe is lightly pressed against your thighs to obtain images of the muscle.
5. **DXA scan.** This bone density test, known as a DXA scan, uses a special low-radiation x-ray machine. This will inform us about your bone health and the amount of muscle and fat in your body. You will need to lie still for several minutes at a time while the arm of the machine passes over these body regions to measure the thickness of your bones.
6. If you are able to take acetaminophen (Tylenol®) (e.g. if, you have no liver abnormalities), you will be given acetaminophen (two 500 mg tablets, to be taken by mouth) 1 hour before the IV infusion, and then you may continue to take it if needed every 8 hours for the next 72 hours to manage possible flulike symptoms such as fever.
7. You will receive the **study drug** (zoledronic acid 5 mg IV or Denosumab 60 mg sc) plus the placebo (e.g., salt water, sugar water)

form of the other medication. This will be given by a nurse or physician's assistant who is a member of the research team. The study drug IV solution will be given through the IV catheter. There is approximately ½ cup of solution which will be given over approximately 60 minutes. After the infusion is complete, the IV catheter will be removed.

8. We will collect your urine sample. You need to be fasting for 8 hours for the urine sample. Because creatine can also be in your urine from food you eat, we ask that you fast, so we only measure the creatine from the capsule. You may also use the urine collection kit to collect your urine sample at home and bring it back to us (needs to be kept in cold temperature).
9. You will receive a second dose of the 30 mg D3-creatine capsule and urine collection kit. The capsule is to be taken **2-4 days (48 to 96 hours) before the Month 12 Visit.** (We may also mail you the D3-creatine capsule and the urine collection kit with their instruction).

Month 6

The Month 12 visit will take a total of approximately 30 minutes. You will receive the **study drug** (Denosumab 60 mg sc or Placebo).

Month 12

The Month 12 visit will take a total of approximately 1 ½ hours of your time for the following procedures:

1. **Brief history** taking.
2. You will be asked about changes in your health since the baseline visit and if you have had any broken bones or falls since then.
3. We will **test your grip strength, balance, and walking.** You may be asked to do things like get up from a chair or walk down a hallway.
4. **Ultrasound**. Ultrasound imaging for this study will obtain images used to measure the thickness and surface area of your thigh muscles. For the ultrasound procedure, you will have ultrasound gel applied to the top of your thigh. You will be asked to straighten your

leg for up to 10 minutes while the ultrasound probe is lightly pressed against your thighs to obtain images of the muscle.

5. We will collect your urine sample. You need to be fasting for 8 hours for the urine sample. Because creatine can also be in your urine from food you eat, we ask that you fast, so we only measure the creatine from the capsule. You may also use the urine collection kit to collect your urine sample at home and bring it back to us (needs to be kept in cold temperature).
6. If you are able to take acetaminophen (Tylenol®) (e.g., if, you have no liver abnormalities), you will be given acetaminophen (two 500 mg tablets, to be taken by mouth) 1 hour before the IV infusion, and then you may continue to take it if needed every 8 hours for the next 72 hours to manage possible flulike symptoms such as fever.
7. You will receive the **study drug** (zoledronic acid 5 mg IV). This will be given by a nurse or physician's assistant who is a member of the research team. The study drug IV solution will be given through the IV catheter. There is approximately ½ cup of solution which will be given over approximately 60 minutes. After the infusion is complete, the IV catheter will be removed.
8. **DXA scan.** This bone density test, known as a DXA scan, uses a special low-radiation x-ray machine. This will inform us about your bone health and the amount of muscle and fat in your body. You will need to lie still for several minutes at a time while the arm of the machine passes over these body regions to measure the thickness of your bones.

You are going to receive telephone call reminders or message on your Epic medical record application regarding information about your upcoming appointments, the need to take the D3-creatine 2-4 days before the baseline visit and again before the 12- month visit.

We will provide you with vouchers for your parking for the baseline, month 6 and month 12 visits.

Additional information on study risks:

Risks of the Study Drug. As with any drug, there may be adverse events or side effects that are currently unknown, and it possible that certain of these unknown risks could be permanent, serious, or life-threatening.

Denosumab:

- The most common side effects for postmenopausal women are back pain, pain in your arms and legs, high cholesterol, muscle pain, and bladder infection.

Other side effects:

- Allergic reactions may occur. Symptoms of a serious allergic reaction may include low blood pressure; trouble breathing; throat tightness; swelling of your face, lips, or tongue; rash, itching, or hives.
- Low calcium levels in your blood (hypocalcemia). The study doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take denosumab. Take the calcium and vitamin D as your study doctor tells you to do.
- Serious infections in your skin, lower stomach area (abdomen), bladder, or ear may happen. Inflammation of the inner lining of the heart (endocarditis) due to an infection may also happen more often in people who take denosumab. Denosumab may affect the ability of your body to fight infections. People who have weakened immune systems or take medications that affect the immune system may have an increased risk for developing serious infections.

Uncommon side effects:

- Increased risk of broken bones after stopping denosumab. After your treatment denosumab is stopped, your risk for breaking bones, including bones in your spine, is increased. Your risk of having more than 1 broken bone in your spine is increased if you have already had a broken bone in your spine. Do not stop taking denosumab without first talking with your doctor. If your denosumab treatment is stopped, talk to your doctor about other medicine that you can take.
- As a safety measure to try to reduce the risk of increased fracture after stopping denosumab, at the month 12 of the study we will provide you with one dose of zoledronic acid 5 mg intravenous.

Rare side effects:

- Severe jaw bone problems (osteonecrosis). You should let your study doctor know if you are scheduled for a tooth extraction before receiving the study drug. It is important for you to practice good mouth care during treatment with denosumab.
- Unusual thigh bone fractures. Tell your study doctor if you have new or unusual pain in your hip, groin, or thigh.
- You should not receive denosumab if you are already receiving a medicine called Xgeva because it contains denosumab. Do not take denosumab if you have low levels of calcium in your blood or have a history of allergic reaction to denosumab.
- Calcium and vitamin D supplements: Mild constipation from the calcium supplement occurs commonly. This may be eliminated by adding fiber to your diet. There are no known side effects for vitamin D when taken within the recommended daily allowance of 800 IU, or up to 4000 IU daily. You will receive calcium and vitamin D supplements as needed based on your dietary calcium questionnaire to achieve at total of approximately 1200 mg calcium daily (dietary plus supplement) and 800-1000 IU vitamin D daily (dietary plus supplement).

Zoledronic Acid:

- The most common side effects are fever; pain in your bones, joints or muscles; pain in your arms and legs, and headache.
- Other side effects include flu-like symptoms (fever, chills, bone, joint, or muscle pain, fatigue), nausea, vomiting, and diarrhea. The majority of flu-like symptoms occurs within 3 days following the dose of zoledronic acid and usually lasts about 3 days but can last up to 7-14 days. These temporary fever and flu-like symptoms can be treated with acetaminophen (Tylenol) to be taken every 6 hours, as needed, for 72 hours following the IV study drug, for participants who are able to take acetaminophen.
- Allergic reactions, such as hives, swelling of your face, lips, tongue, or throat may occur. A rare side effect is eye inflammation. Serious and rare side effects can include:

- Low calcium levels in your blood (hypocalcemia). The study doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take zoledronic acid. Take the calcium and vitamin D as your study doctor tells you to do.
- Severe kidney problems. You should drink at least 2 glasses of fluid within a few hours before receiving zoledronic acid to reduce the risk of kidney problems.
- Severe jaw bone problems (osteonecrosis). You should let your study doctor know if you are scheduled for a tooth extraction before receiving the study drug. It is important for you to practice good mouth care during treatment with zoledronic acid.
- Unusual thigh bone fractures. Tell your study doctor if you have new or unusual pain in your hip, groin, or thigh.
- You should not receive zoledronic acid if you are already receiving Zometa® or Reclast® because both Reclast® and Zometa® contain zoledronic acid. Do not take zoledronic acid if you have low levels of calcium in your blood, have kidney problems, or have a history of allergic reaction to bisphosphonates (such as Fosamax® and Actonel®).

Other Risks:

- Risk of Intravenous (IV) line placement: The risks of IV insertion may include pain, infection, inflammation of the vein (phlebitis), and IV fluid accidentally entering the surrounding tissue (infiltration).

- Acetaminophen Risks: Common side effects include itchiness or rash, constipation, nausea, and vomiting. Serious side effects include liver failure.

- Risks of the D3-creatine: As with any supplement, there may be adverse events or side effects that are currently unknown, and it possible that certain of these unknown risks could be permanent, serious, or life-threatening. Some participants may also experience difficulty swallowing the capsule (choking) similar to any other capsule.

- Participation in this research study will involve radiation exposure: Participation in this research study screening will involve radiation exposure from the dual-energy x-ray absorptiometry (DXA) scans. Participants will have DXA scans of their spine (front and side), vertebral

fracture assessment (VFA), hip (total hip), forearm, and total body. If they complete the screening DXA scans as outlined in the protocol, the total radiation dose to the spine will be about 80 mrems (an mrem is a unit of radiation). For the baseline screening, the radiation dose to the hip will be about 10 mrems. The radiation dose to the wrist will be about 10 mrems, and the radiation dose to the total body will be about 1 mrem. For the 1 year follow up, the total radiation dose to the spine will be about 320 mrems (an mrem is a unit of radiation). The radiation dose to the hip will be about 40 mrems. The radiation dose to the wrist will be about 40 mrems, and the radiation dose to the total body will be about 4 mrems. For comparison, these radiation doses are a very small fraction of the maximum annual whole body radiation dose (5000 mrems) permitted by federal regulation to adult radiation workers. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (cellular abnormalities) or cancer. However, the risk associated with the amount of radiation exposure from participation in this screening is considered to be low and comparable to everyday risks.

- Walking and Balance tests: There is a risk of falling or of discomfort (pain) while doing the walking and balance tests. The study coordinator is trained to intervene to prevent a fall from happening. You can decline to do any of the balance or walking tests that you do not want to do or that you feel is too painful. To protect your privacy, these tests will be done in a private room except for the walking test, which may be done in a cleared hallway.

- Collection and storage of personal health information and biospecimens: The risks of collecting and storing your personal health information and storing your samples long-term is breach of confidentiality.

What treatments or procedures are available if you decide not to take part in this study?

You may choose not to participate in this research study. You may discuss other methods to evaluate physical function, or measurements of your body's composition of muscle and bone quality with your physician.

Evaluations of physical function and muscle mass are available outside of this study.

None of the tests or procedures done for research study purposes will be billed to you or your health insurance (physical assessments and questionnaires, DXA, muscle ultrasound, D3-creatine capsules, urine collection kit). If you receive a bill or believe your health insurance has been billed for something that is part of the research study, notify the study coordinator as soon as possible.

Other tests and procedures that would normally be done as part of your conventional care will be your responsibility and charged to you or your health insurance, in the standard manner, for services and procedures that are done as part of your routine care including blood work or cost of medications used for treatment of osteoporosis. Any deductible or copayments that are part of your insurance coverage will apply.

If you believe that the research study procedures have resulted in an injury to you, immediately contact the Principal Investigator or Study Coordinator (see first page for contact info). Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of follow-up care. At this time, there is no plan for any additional financial compensation. You do not waive any rights by signing this form.

Will this research study involve the use or disclosure of my identifiable medical information?

As part of this research study, we are asking your permission to use your medical records to see if you are eligible to be in this study, to compare your earlier test results to the findings from this study as well as to support other data collected in the study. This permission does not expire. We will collect the following information: your diagnosis, age, past medical history, tests that were done to diagnose your condition, and results of any tissue biopsies or blood tests, including results of genetic tests that were already done as part of your standard medical care.

This medical record information, which includes your name, is available to members of the research team for an indefinite period.

Your ultrasound, D3-creatine, functional evaluation results and response to questionnaires will be entered in your Osteoporosis Prevention and Treatment Center medical record.

Your DXA report will be placed in the medical record

To protect your privacy and maintain the confidentiality of information we obtain from you and from your medical records, we will keep all information about you in a secure location.

All paper records that could identify you will be stored in a locked file cabinet, and all electronic records will be stored in password-protected files. Your identity on these records will be indicated by a case number rather than your name, and the code linking your name to this number will be maintained separately with very limited access by research team members.

Although we will do everything in our power to protect your privacy and the confidentiality of your records, just as with the use of your medical information for health care purposes, we cannot guarantee the confidentiality of your research records, including information that we obtained from your medical records.

Your research information, specimens and data may be shared with investigators conducting other research in the future. This information will be de-identified.

In addition to the investigators listed on the first page of this consent document and their research team, the following individuals may have access to your identifiable medical information related to this research study:

- UPMC hospitals may have access to identifiable information only for the purposes of (1) filling orders made by the researchers for hospital and health care services (e.g., laboratory tests) associated with the study, (2) addressing correct payment for tests and procedures ordered by the researchers, and/or (3) for internal hospital operations (e.g., quality assurance).

- Authorized representatives of the University of Pittsburgh Office of Research Protections and the sponsor, the National Institutes of Health may review your identifiable research information for the purpose of monitoring the appropriate conduct of this research study.
- Authorized representatives of the sponsor(s) of this research study (see page 2), such as outside laboratories assaying urine samples, may review and/or obtain identifiable information related to your participation in this study for the purposes of monitoring the accuracy and completeness of the research data and for performing requires scientific analyses of the research data.
- If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform the appropriate agencies as required by law.

Your data or specimens used in this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or outside agencies may receive.

According to University of Pittsburgh policy, **all research records must be maintained for at least 7 years following the final reporting or publication of a project.**

Your doctor may be involved as an investigator in this research study, but you are not under any obligation to participate in any research study offered by your doctor. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of the research study. Before agreeing to participate in this research study, or at any time thereafter, you may wish to discuss participation with another health professional that is not associated with the research.

Your participation in this research study is completely voluntary.

You may want to discuss this research study with your family and friends and your personal physician before agreeing to participate. If there are any

words you do not understand, feel free to ask us. The investigators will be available to answer your current or future questions. Whether or not you participate will have no effect on your current or future relationship with the University of Pittsburgh, UPMC, or its affiliated health care providers or health insurance providers.

You will be notified of any results that might affect your personal health or decisions. You will be promptly notified if any new information we learn during this research study may cause you to change your mind about continuing to participate in the study.

If you decide you no longer wish to participate after you have signed the consent form, you should contact the principal investigator or the research coordinator (contact info on page 1). **To formally withdraw your consent for participation, you should provide a written and dated notice of this decision to the principal investigator** listed on the first page of this form. You may also withdraw, at any time, your authorization to allow the research team to review your medical records, but if you do so, you will no longer be able to participate in this research study. Any information obtained from you up to that point, however, will continue to be used by the research team. Your decision to withdraw from this research study will have no effect on your current or future relationship with the University of Pittsburgh or with UPMC or its affiliated health care and insurance operations.

The investigators may withdraw you from the research study if they feel that you cannot complete the study requirements safely (for example, if you need other treatment, cannot undergo the study procedures, do not follow the investigators' instructions, experience adverse events).

You might also be removed from the research study for other medical or administrative reasons (for example, the research resources are no longer available or no longer funded by the research sponsor). We will notify you should this arise and advise you if there are available alternatives that may be of benefit at the time.

Clinically relevant research results, including individual research results, will be verbally disclosed to you by the registered nurse or physician investigators at the end of the study.

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Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that any future questions, concerns, or complaints will be answered by a qualified member of the research team listed on the first page of this consent document at the telephone numbers given. I understand that I may always request that my questions, concerns or

complaints be addressed by a listed investigator. At any time I may also contact the Human Subjects Protection Advocate of the Human Research Protection office at the IRB Office, University of Pittsburgh (toll-free at 1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable. **By signing this form, I agree to participate in this research study and allow the use and disclosure of my medical record information for the purposes described above.** A copy of this consent form will be given to me.

_____ _____

Participant's Signature Date

_____

Participant's Name (Print)

VERIFICATION OF EXPLANATION:

I certify that I have carefully explained the purpose and nature of this research study to the above-named participant in appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she has provided affirmative agreement (i.e., assent) to participate in this study.

_____ _____

Investigator's Signature Date and Time