COVER PAGE

STUDY TITLE: Creatine Use and Muscle Stretching in Peripheral Artery Disease

NCT Number: NCT04471792

Date Consent Approved: 04-02-2022

Consent Document to follow

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CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Creatine Supplementation and Muscle Stretching in Peripheral Artery Disease

Principal Investigator: Judy Muller-Delp

Introduction

We invite you to take part in a research study at Florida State University.

Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone on the FSU research team, or with family, friends or your personal physician or other professional.

First, we want you to know that:

Taking part in research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of research procedures they would want to receive. If you have such beliefs, please discuss them with the research team before you agree to the study.

Key information about the research study

Things you should know:

The purpose of the study is to investigate the impact of creatine supplementation on walking performance. If you choose to participate, you will be asked to complete two individual days of testing at FSU, College of Medicine. You will use an investigational splinting device to stretch the calves 30 minutes/day five days/week for four weeks. In addition, you will be placed into either the treatment or no treatment group (creatine versus no creatine). In total, this investigation will take about 5 weeks to complete.

- Risks or discomforts from this research include stomach upset from creatine or fiber ingestion and/or muscle discomfort during the stretching protocol.

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Abnormally elevated heart rate, breathing and leg pain may be present during the walking test. If you have a history of renal disease, you will not be able to participate in the current study.

- Magnetic Resonance Imaging (MRI) risks. Some people who are in this study will have an MRI at their second and third visits, but not everyone. While there are no known permanent negative effects from exposure to a strong magnetic field, there may be some temporary one. These temporary effects may include dizziness, nausea or a metallic taste in your mouth. Some pulse sequences can cause temporary peripheral nerve stimulation which causes mild discomfort but is not harmful. Some pulse sequences can cause heating of your body. If you experience any discomfort that you cannot tolerate, you will be given an alarm bell to notify researchers that you would like to discontinue the study. MRI produces very loud pulsating sounds. You will be required to wear earplugs or a headset to protect your hearing.

- The study may lead to improvements in activities of daily living in patients that cannot exercise without leg pain.

- **Taking part in this research project is voluntary**. You don't have to participate, and you can stop at any time.

Please take time to read this entire form and ask questions before deciding whether to take part in this research project.

Why is this study being done?

This study is being conducted by Judy Muller-Delp, PhD, Jacob Caldwell, PhD. Drs. Muller-Delp and Caldwell are researchers in the Department of Biomedical Sciences at FSU College of Medicine. The current study is funded by FSU.

The purpose of the current investigation is to see if four weeks of creatine supplementation improves vascular function and walking performance in patients with peripheral artery disease versus healthy controls.

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Why are you being asked to take part in this study?

You are being asked to take part in this study because you either have a diagnosis that is consistent with peripheral artery disease or you are a healthy control participant.

How many people are expected to take part in this study?

About fifty participants with and without peripheral artery disease (men and women, 40-95 years old) will be recruited for this study.

Before you begin the study

If you are interested in participating in this study, you will be asked to complete and sign this informed consent and health history, and doctor release forms. This signed informed consent will be proof of enrollment as a prospective participant and your second visit will be scheduled. We will also obtain physician clearance from your doctor if you have been diagnosed with peripheral artery disease. You will not be able to begin the study if your cardiologist or primary care physician does not sign off allowing you to participate. If you are a healthy control, no doctor's approval will be needed.

Inclusion checklist:
1) Ankle-brachial index (ABI), a blood pressure ratio between the ankle and brachial arteries, of 0.90 or less (PAD group only and confirmed by physician)
2) Stable condition for at least 3 months (PAD group only)
3) Ages 40-95
4) Ability to speak and read English
5) No cardiovascular disease (healthy volunteers only)

Exclusion checklist (PAD and Healthy Volunteers):
1) Habitual exercise or cardiovascular rehabilitation program during the past 3 months
2) Critical limb ischemia
3) Amputation
4) Leg pain at rest
5) Major surgery or lower extremity revascularization in the last 3 months
6) Major medical illness treatment during the prior 12 months

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7) Central neurological disease
8) Joint or muscle range of motion issues
9) Requirement of supplemental oxygen
10) Heart Failure
11) Atrial fibrillation
12) Wheelchair confinement or inability to walk
13) Overt cardiovascular disease
14) Takayasu's arteritis, Berger's disease, collagen disease, or Reynaud's disease
15) Metabolic disease
16) Kidney disease

Things that will eliminate your ability to do an MRI, but will not remove you from this study:
1) Pacemaker or pacer wires
2) Open heart surgery
3) Artificial heart valves
4) Aortic aneurysm clips
5) Cochlear implants (hearing device)
6) Braces or extensive dental work
7) Implanted electrical or mechanical devices
8) Tissue expanders
9) Foreign metal objects from explosives
10) Shrapnel or metalwork fragments in eyes/skin/body
11) Artificial limbs
12) Currently pregnant or lactating
13) Claustrophobic
14) Have tremors or cannot lie still for 1-2 hours
15) History of being a metal worker/welder
16) History of eye surgery/eyes washed out because of metal
17) Birth control devices (I.U.D.)
18) A shunt (ventricular or spinal)
19) Metal plates/pins/screws/wires
20) Neuro/bio-stimulators (TENS unit)
21) Vision problems uncorrectable with lenses

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22) Prior neurosurgery
23) Older tattoos with metal dyes
24) Unwillingness to remove nose, ear, tongue or face jewelry

Study procedures

If you agree and are eligible to participate in this study, we will ask you to do the following: You will be randomly assigned to one of two groups: a stretch group plus supplement or a stretch group plus placebo supplement (fiber pills). All participants will perform 30 minutes of muscle stretching, 5 days/week for 4 weeks using a study-provided splint device. The calf muscles will be stretched by wearing splints that will position the ankle at an angle that will produce maximal muscle stretch of the calf muscles without causing major discomfort. You will be assigned to one of two supplement groups: 1) consuming 10 grams/day of creatine for five days and then a maintenance dose of 5 grams/day, or 2) consuming 10 grams/day of fiber (no creatine) and then a maintenance dose of 5 grams/day. Both supplements will be taken for 4 weeks.

Supplementation specifics: You will consume either creatine (General Nutrition Center, GNC) or dietary fiber powder (Allergy Research Group, ARG) that has been provided to you. Each day you will measure out **10 grams per day for 5 days and then 5 grams per day for the remainder** of the study (23 days). We will provide you with the supplements and walk you through measurement with the provided teaspoon. We suggest mixing the powder in juice or milk. An instruction sheet will be provided to you that talks about how to measure and consume the supplement each day.

There will be three visits for this study. Visit 1 is to qualify you for this study. Visit 2 is your baseline visit and Visit 3 is the visit you do after you have taken your supplement and stretched for about 4 weeks.

In either healthy control or patient group, your first study visit will include signing this consent form and completing a few surveys. You will also receive a Fitbit at visit 1 and visit 3 to wear for 1 week to monitor daily step count. If you are in the PAD group, you will then have to get your doctor's permission to participate in Visits 2 and 3. You will then make two visits, about a month apart, to FSU to complete pre- and- post

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measurements and some more surveys. We ask that you not change your lifestyle (diet, exercise, medicine) during the 4-week study period as much as possible.

Our research team will ask you for your health information, including medical history and an exercise questionnaire. Ankle-brachial index (ABI) information will be taken from your cardiologist if he or she agrees to let you participate. When you come to the FSU College of Medicine lab for Visits 2 and 3, fasting is required for at least four hours and we also ask that you refrain from caffeine and excessive physical activity for 24 hours prior to the visit.

After your eligibility for inclusion in this study is confirmed, you will be asked to complete a subject contact information, health history and Physical Activity Questionnaire, SF-36, and the Walking Impairment Questionnaire (WIQ). Your body weight, height, waist and lower leg circumference, ankle and knee range of motion will be measured.

We will then place a blood oxygenation monitor on your leg and you will be taught how to set up and use the muscle stretching device. Next, you perform one test to assess blood vessel function and one test to stretch your calf. Next, if you qualify for an MRI and are selected to do one, you will be placed in the MRI scanner for approximately 1 hour. Once set up and laying on your back in the MRI you will go through a baseline measurement followed by lower leg occlusion and another resting condition. Next, we will use the splint device to stretch your muscle and measure blood flow during and after the stretch.

After the MRI measurements, we will set up our blood oxygenation monitor on your leg during 5 min of rest while you are sitting upright in a chair. Following this, you will perform an 8 foot up and go test. During this test, you will start in a seated position, stand up, walk 8 feet, then return to the seated position. The score for this assessment will be the number of seconds needed to complete this task. You will perform this assessment twice, and the best score of the two trials will be used.

A six-minute walking test will be performed next. Specifically, in the six-minute walk test you will walk back-and-forth continuously down a 33 yard hallway, covering as much ground as possible during 6 minutes. During this test we will ask you about how hard you feel like you are working and provide you with a pain scale. If you reach a

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grade greater than 3 (mild pain) on a scale up to 5 (severe pain) on the pain scale (see figure 1) you will be asked to stop and rest and the walking test will not continue.

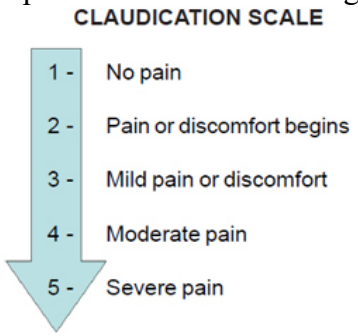

Figure 1.

Following a rest period after the six-minute walk test, you will perform a 30 second chair rise test. In this assessment, the number of full stands from a seated position will be counted in the 30-second time period.

Next you will perform a chair sit and reach test. This test will require you to reach your fingertips towards a straightened leg from a seated position. This assessment will be performed three times on each leg. The final task will be a 1minute heel raise test.

After testing is complete, you will be asked if you have any other questions about how to set up and use the muscle stretching device. You will be stretching both calves for 30-minutes per day, five days per week. The stretching will be performed at home during a seated resting condition with your feet placed up on a leg rest or support.

How long will I be in this study?

The current study will take about 5 weeks to complete. We anticipate each visit to FSU will take 2-3.5 hours to complete.

Risks of study participation

The study has the following risks:

- Being uncomfortable answering the questions or completing the study tasks**.** While completing any of the questionnaires or tasks, you can tell the researcher that you feel uncomfortable or do not care to answer a specific question or if you want to stop any tasks.
- Being tired or fatigued during the battery of tasks and questionnaires. Let the researcher you are working with know if you are feeling tired or fatigued and need to take a break.
- Feeling frustrated with the tasks and/or questionnaires. Some questions or tasks may seem hard to you, and that is okay. Just answer the questions and perform the tasks the best you can.
- Possible loss of confidentiality, although we have safeguards in place to protect your confidentiality.

While there are no known permanent negative effects from exposure to a strong magnetic field of an MRI machine, there may be some temporary ones. These temporary effects may include:

- Dizziness
- Nausea
- Metallic taste in your mouth.

Some types of MRI scan can cause temporary peripheral nerve stimulation which causes mild discomfort but is not harmful. Some types of MRI scan can cause heating of your body. If you experience any discomfort that you cannot tolerate, you will be given an alarm bell to notify researchers that you would like to discontinue the study.
MRI produces very loud pulsating sounds. You will be required to wear earplugs or a headset to protect your hearing.

There is a minimal level of risk involved in participating in the muscle stretching program. You could experience leg pain or cramping during muscle stretching, however this is very unlikely. These possible effects of muscle stretching should disappear within a few minutes after the termination of the muscle stretching. You should remove the splint and rest if any intolerable leg pain occurs during muscle stretching. We are currently unaware of any risk of blood clot during use of the splint device.

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There is a minimal level of risk involved with blood pressure cuff inflation during the muscle oxygenation measurement and blood vessel function test. There could be local discomfort, moderate pain, tingling and temporary numbness. These possible effects of blood pressure cuff inflation will disappear within a few minutes after the termination of the test. Creatine supplementation is widely used and there are no apparent cardiovascular related risks that we are aware of. However, there is some concern that creatine could make kidney disease worse, which is why you cannot be in this study if you have kidney disease. You may experience slight stomach upset or water weight gain during supplementation that will cease once the protocol is over. If you are in the non-treatment group, the side effects of the fiber are gas, bloating, diarrhea, dehydration, and weight gain. We are aware of no other side effects of the placebo treatment.

There is a minimal risk of skin irritation while wearing the Fitbit. To reduce this risk, it is recommended you keep the device clean, dry, and to not wear the device too tightly. If skin irritation occurs and does not resolve within 3 days, discontinue use of the device. If any soreness, tingling, numbness, burning, or stiffness in the hands occurs in the hands or wrists, subjects will be instructed to discontinue use of the device immediately. To reduce the risk of the preceding, we recommend the following:

1. Do not attempt to replace the battery, open the enclosure or disassemble your Fitbit product.
2. Do not use your Fitbit product if the display is cracked.
3. Do not expose your Fitbit product to extremely high or low temperatures.
4. Do not use your Fitbit product in a sauna or steam room.
5. Do not use abrasive cleaners to clean your Fitbit product.
6. Remove your Fitbit product immediately if it feels warm or hot.
7. Charge the battery with the charging cable provided. Do not use other cables.
8. Do not wear your Fitbit product while charging it.
9. Do not charge your Fitbit product while it is wet.

Summary of Risks:
Healthy control: uncomfortable muscle stretch and blood pressure cuff.
Placebo: uncomfortable muscle stretch, blood pressure response to walking, bloating, gas, diarrhea.

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Creatine: uncomfortable muscle stretch, blood pressure response to walking, bloating, gas, diarrhea, dehydration, and weight gain.

Peripheral Artery Disease Patients: uncomfortable muscle stretch and blood pressure cuff, skin irritation
Placebo: uncomfortable muscle stretch, blood pressure response to walking, bloating, gas, diarrhea.
Creatine: uncomfortable muscle stretch, blood pressure response to walking, bloating, gas, diarrhea, dehydration, and weight gain.

However, because this is a research study, there may be additional risks that we cannot identify at this time.

Benefits of study participation

The benefits to study participation are potential improvements of blood vessel function, skeletal muscle oxygenation, and walking performance in participants who undergo 4 weeks of muscle stretching plus creatine supplementation. All patients will receive assessment of blood vessel function, walking performance and anthropometry free of charge.

Summary of Benefits:
Healthy control: None
Peripheral Artery Disease Patients:
Placebo: increasing functional capacity and cardiovascular health outcomes.
Creatine: increasing muscle blood flow, increasing functional capacity and cardiovascular health outcomes.

Alternatives to study participation

The current study is voluntary, and you can withdraw from the study at any time. The only alternative is not to participate in the study.

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Ending the study

At any time during the study you may opt out and discontinue without any consequence to you. The investigation is totally voluntary. In certain cases, we may ask you to discontinue stretching. This usually happens only when you choose to stop. We may also stop you from being in this study if you don't continue to follow the stretching or supplementation protocol.

Study costs/compensation

There will be no costs to participate in this study. Splint devices and supplements will be provided to you. You will only be expected to pay for the costs of your transportation to and from FSU. You will receive a payment of $100 only after you complete all study visits.

Research Related Injury

There are no further research related risks of injury in addition to the highlighted risks above in the Risks of Study Participation section. In the event you suffer from an injury, investigators will have access to first aid and emergency services if needed and medical doctors are located in the building where the research activities take place. This will be insured by a plan of action in place, of which all investigators will be informed. Investigators will follow up with any participant that suffers from an injury, and ensure the best standard of care is provided.

If you feel like you have been hurt or injured because of something that is done during the study, you should immediately contact Dr. Judy Delp, PhD, at 352-226-9535. Costs associated with any care that may be needed post-injury will be billed in the ordinary manner, to you or your insurance company. However, some insurance companies will not pay bills that are related to research costs. You should check with your insurance about this. Medical costs that result from research-related harm may also not qualify for payments through Medicare, or Medicaid.

Who can profit from study results?

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No financial conflicts or gains have been identified in connection with this study for the study team with the exception of the principal investigator, Dr. Judy Delp. She has a potential use patent with Florida State University on the splinting device used in this study. The patent application is currently in progress.

How Will My Samples and Data be Used?

All data collected will be entered into an electronic database called REDCap which is managed by FSU College of Medicine. Your data will be stored in a HIPAA compliant environment, which means that your health information will be well-protected. The study data will only be accessible by the study team and principal investigator. All non-electronic data on paper (surveys and forms that you complete) will be stored in a locked cabinet that only the research team has access to. Your data will be kept to the extent permitted by the IRB and the FDA. If you choose, you may voluntarily stop participation at any time before the study has finished. In this circumstance all data collection will be discontinued, but data collected up to the time you stopped may be used.

Confidentiality

The records of this study will be kept private and confidential. Any personal data that is collected fully protected via the use of encrypted coding and passwords. All data collected in hardcopy form (for example, consents and questionnaire responses) will be kept securely under lock and key, with access only available to the PI. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. If during any point of the statistical analysis data is sent via the internet to another investigator, all data will be protected by the same encrypted code, with no personal identifiers being used.

Will my medical/health information be kept private?

Your protected health information (PHI) created or received for the purposes of this study is protected under the federal regulations known as HIPAA. Refer to the HIPAA authorization for details concerning the use of this information.

Protected Health Information (PHI):

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Study staff will record your email address, telephone number and name for the purpose of scheduling day and time of the pre- and post- visits. This information will be kept in REDCap but in a separate page from the other information in the database. It will only be available to members of the study team who need to contact you. The rest of your study information will be linked to a study code number in order to protect against disclosure of your information. Information obtained during the course of the study will remain confidential. Your name will not appear on any of the results. No individual responses will be reported. Only group findings will be reported in publications.

Voluntary Nature of the Study

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Contact information for questions about your rights as a research participant

If you have any questions or concerns about your rights as a research participant, or regarding the study and would like to talk to someone other than the researcher(s), you are encouraged to contact the FSU IRB at telephone number 850-644-7900. You may also contact this office by email at humansubjects@fsu.edu, or by writing or in person at 2010 Levy Street, Research Building B, Suite 276, FSU Human Subjects Committee, Tallahassee, FL 32306-2742.

You will be given a copy of this form for your records.

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Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in this study.

_____	_____
Signature of Participant	Date
_____	_____
Printed Name of Participant	Date
_____	_____
Person Obtaining Consent	Date