Document Coversheet

Study Title: Mechanisms Underlying Local and Systemic Effects of Massage

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Combined Consent and Authorization to Participate in a Research Study

THE CELLULAR EFFECTS OF MASSAGE ON HUMAN SKELETAL MUSCLE TISSUE

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS RESEARCH?

You are being invited to take part in a research study about the effects of massage on the cellular responses of muscle. You are being invited to take part in this research study because you are a healthy individual between the ages of 18 to 30. If you volunteer to take part in this study, you will be one of about 140 people to do so at the University of Kentucky.

WHO IS DOING THE STUDY?

The person in charge of this study is Esther Dupont-Versteegen, PhD (Principal Investigator, PI) of University of Kentucky, Department of Rehabilitation Sciences. There may be other people on the research team assisting at different times during the study.

WHAT IS THE PURPOSE OF THIS STUDY?

By doing this study, we hope to learn more about how muscle cellular properties are changed by massage.

ARE THERE REASONS WHY YOU SHOULD NOT TAKE PART IN THIS STUDY?

You should not participate in this study if you:

- Are under the age of 18 or over the age of 30
- BMI over 27
- Have current lower extremity musculoskeletal injuries
- Have had previous lower extremity surgeries or injury
- Activities of daily living require long periods of standing or driving a manual transmission car.
- Evidence or signs and symptoms of metabolic syndrome or disorder (diagnosis of diabetes or insulin resistance, elevated BP, high fasting blood sugar, abnormal cholesterol or triglyceride levels).
- Thyroid disorder
- Acute or chronic infections
- Use of systemic steroids, anabolic steroids, or growth hormone
- Are currently pregnant
- Have a family history of bleeding problems (“free bleeder"), as evidence by:
    - unexplained nosebleeds (epistaxis)
    - excessive or prolonged menstrual blood flow (menorrhagia)
    - prolonged bleeding after minor cuts, dental procedures, tooth brushing or flossing, or trauma
- Are using medications that increase the risk of bleeding (unless it can be safely stopped):
    - Aspirin
    - Clopidogrel
    - non-steroidal anti-inflammatory drugs
    - any anticoagulation therapy (warfarin or heparin)
- Are allergic to Betadine or Xylocaine HCI.
- Any other condition or events considered exclusionary by the PI and /or physician, such as non-compliance

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

You will be required to come to the College of Health Sciences or CCTS for your initial screening visit, blood draws, and for possibly receiving four massages if you are randomized to the massage group. You may also be required to wear a brace with the use of crutches for a period of one week if you are randomized to the immobilization group. The muscle and blood sample procedures will be conducted in the CCTS located in the UK Chandler Medical Center. You will need to come to the CCTS just two times for the study for those procedures. The total amount of time for these visits to the lab or hospital will be approximately 4 to 4.5 hours over a period of 9 days.

WHAT WILL YOU BE ASKED TO DO?

You will be required to meet with the research team to be placed by chance into a group (normal weight-bearing with massage (WB-M) or without massage (WB-C), unilateral lower limb suspension (ULLS), no massage (control,U-C), and ULLS with massage (U-M)). ULLS involves wearing a knee brace locked in such a position that you will not be able to put weight on the leg, and in addition you will be given crutches. You have a one in four chance to be placed into any group. You will drink heavy water for 9 consecutive days with subsequent blood draws, have your left thigh massaged for 15 minutes every other day (if in massage group) over the course of the last 7 days of the 9 day trial, and have a three muscle biopsies (one on the left leg, and two on the right) taken from the outer side of each thigh. Each muscle biopsy will be taken by a physician or Physician's Assistant under the supervision of a medical doctor. You will be asked to come for a baseline biopsy two days after starting the heavy water, which will last 1 hour and will then be asked to be massaged for 15 minutes every other day over the course of the next 7 days. The massage treatments will be held in room B04A in the Multidisciplinary building (Human Performance Lab). On the last day (day 9), a biopsy will be taken 4 hours after the last massage. Subjects in the 9 day trial will have to intake deuterium oxide ($^2H20$} heavy water throughout the whole study which will also involve a total of 3-4 subsequent blood draws.

If you are randomized to one of the weight bearing groups, you will also have to drink deuterium oxide heavy water over 9 days which is associated with 3-4 blood draws but will not have to wear a brace or use crutches. Weight bearing control groups will only have one biopsy taken on day 9 while weight bearing massage groups will have two biopsies taken (day 2- right leg, and day 9- left massaged leg).

Cyclic Compressive Loading (CCL) Device Reliability and Validity Testing:
Forty participants will be requested to participate in pilot testing of the CCL device. This testing will be used to validate the equipment. Two different clinicians will massage all participants for 15 minutes on two separate days. The load applied to the tissue will be measured and compared between clinicians and days. This will allow analysis of inter-rater reliability and test-retest reliability. The same inclusion and exclusion criteria will be used as in the original study.

Medical Health Questionnaire
You will be asked questions about your health to ensure you are eligible for this study.

Heavy Water $^2H20$ (9 days):
Deuterium oxide or heavy water ($^2H20$) is used to measure the addition of new protein to muscle. It is a stable, non-radioactive isotope that is indistinguishable from normal water. It is simply water that has a higher amount of a natural, but less abundant, form of hydrogen. You will be required to ingest the heavy water for 9 days. You will be sent home with 50 ml(= 1/4 cup) doses of heavy water in sealed sterile vials. The first two days, you will consume one 50 ml vial of the heavy water three times a day (150 ml/day). The next 7 days, you will consume one 50 ml vial twice a day (100 ml/day). This will total 1000 ml of water per subject.

Blood draws:
Over the course of the 9 day trial, your blood will be drawn 3-4 times on days 2, 5, 7, and 9 to be used in measuring protein synthesis and small circulating molecules called micro-RNAs.

Immobilization (7 days):
Participants of the U-M and U-C groups will be placed in a knee immobilizer locked between 30-50 degrees of flexion on their left leg and will be provided with fitted crutches. You will be instructed in appropriate crutch use and fitting of the brace as to ensure proper training in the use of the equipment. Participants in U-M and U-C

groups will be non-weightbearing starting on day 2 (after the first two days of heavy water intake) of the 9 day trial for a total of 7 days. These participants will be expected to wear the immobilizer and use the crutches at all times, except while showering and sleeping. They will also be required to log and explain on the attached Immobilization Time Log any time they did not use or wear the crutches or knee immobilizer in order to track compliance.

Massage or Sham Treatment (15 minutes, 4 days):
After the baseline muscle biopsy is complete on the right thigh on day 2 of the trial, a custom-made cyclic compressive loading (CCL) device will be used to manually apply a mechanical load to the left thigh of those in the WB-M and U-M groups. A 35 Newton (8-pound) load will be applied for 15 minutes every other day over the course of 7 days (days 3, 5, 7, and 9). If you are in the WB-C or U-C groups, we will touch your skin using a light brushing technique to be used as a control.

Muscle Biopsy (45 minutes for the first biopsy and 90 minutes for the second two biopsies):
A small piece of your muscle tissue will be removed from each thigh. The muscle tissue will be taken from your . vastus lateralis muscle which is located on the outside of your thigh and will be taken about one hand width above your knee. A 1 inch by 1inch area will possibly need to be shaved if necessary. You will then have this area of your thigh numbed with an injected anesthetic (Xylocaine) and a small 1/4 inch incision will be made in the skin. A needle or conchotome (a tissue cutting device) will then be briefly (lasting just a couple of seconds) inserted into the muscle to remove a 100-300 mg piece of muscle (about the size of a pencil eraser). The incision will be closed according to standard procedure after the site is cleaned with an alcohol preparation and your leg will be wrapped snuggly with an elastic bandage. You will be provided with some easy take home biopsy care instructions. During the COVID-19 pandemic, you will be asked to provide evidence of a negative COVID-19 test before having this procedure done.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

You have been told that this study may involve the following risks and/or discomforts:

Muscle Biopsy
With the biopsy procedure, there is a risk of bleeding, bruising, soreness, pain, infection, and scarring of the skin. Bleeding could rarely result in development of a hematoma (deep tissue collection of blood). Pain and soreness usually resolves within 24-48 hrs post-procedure. Numbness of the skin, about the size of a coin, near the biopsy site may occur and is usually temporary, but this numbness may persist indefinitely. An allergic reaction to the anesthetic also may occur but is rarely seen. If you are required to have COVID-19 testing, this test can be uncomfortable as with any nose swab.

Muscle Biopsy

Possible Risk/SideEffect	How often has it	How serious is it?	Can it be corrected?
Soreness	it usually occurs	Can be treated	It will go away with or without treatment within 24-48 hrs in most cases
Pain	It often occurs	Does not impact your overall health and can be treated	It will go away within 24-48 hrs in most cases
Bleeding	It occasionally occurs and sometimes can lead to a hematoma (deep tissue collection of blood)	Can be treated and hematoma will resolve on its own	Yes, by applying pressure
Bruising	It occasionally occurs	Treatment is notrequired	Yes, itwill fade on Its own

Fainting	It is uncommon	Can be easily treated by lying down with the leas elevated	Yes, usually in 20 minutes
Infection	It is very uncommon	Can be treated	Yes
Numbness at the biopsy site	It occasionally occurs	Does not impact your overall health and treatment is not required	Can persist in rare cases
Scarring	It occasionally occurs	Does not impact your overall health	Can persist

Massage

Possible Risk/Side Effect	How often has It occurred?	How serious is it?	Can it be corrected?
Soreness	It usually occurs	Does not impact your overall health and treatment is not required	It will go away with or without treatment within 24-48 hrs in most cases

Deuterium Oxide Heavy Water (^2H2O)

Possible Risk/Side Effect	How often has It occurred?	How serious is it?	Can it be corrected?
Dizziness	It usually occurs (after the initial dose)	Can be treated by keeping well hydrated	It will go away with or without treatment

Immobilization/ULLS

Possible Risk/Side Effect	How often has It occurred?	How serious is it?	Can it be corrected?
Soreness on overloaded leg	It usually occurs	Can be treated	It will go away with or without treatment within 24-48 hrs in most cases
Atrophy	It always occurs	Can be treated	Yes
Chaffing	It often occurs	Can be treated	It will go away with or without treatment
Edema	It often occurs	Can be treated	It can be helped by doing foot and ankle exercises

Blood Draws

Possible Risk/Side Effect	How often has It occurred?	How serious is it?	Can it be corrected?
Soreness	It often occurs	Can be treated by keeping well hydrated	It will go away with or without treatment
Bruising	It occasionally occurs	Treatment is not required	Yes, it will fade on its own
Pain	It often occurs	Does not impact your overall health and can be treated	Yes

Infection	It is very uncommon	Can be treated	Yes
Possible Fainting	It is uncommon	Can be easily treated by lying down with the legs elevated	Yes, usually in 20 minutes
Bleeding	It occasionally occurs	Can be treated	Yes, by applying pressure

There is always a chance that any investigational treatment can harm you. In addition to the risks listed above, you may experience a previously unknown risk or side effect.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

You will not benefit from taking part in this study. Your willingness to take part, however, may, in the future, help researchers better understand the response of skeletal muscle to massage at the cellular and molecular level.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any benefits or rights you would normally have if you choose not to volunteer. You can stop at any time during the study and still keep the benefits and rights you had before volunteering. As a student, if you decide not to take part in this study, your choice will have no effect on your academic status or grade in any class.

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to be in the study, there are no other choices except not to take part in the study.

WHAT WILL IT COST YOU TO PARTICIPATE?

The only cost you will experience is your time for participation and travel expenses (gas and mileage) to the University of Kentucky. Parking in the Kentucky Clinic will be validated for the study visit. Therefore, there will be no costs associated with parking for you as long as you park in the Kentucky Clinic parking lots and have your ticket validated by the research team.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

We will make every effort to keep private all research records that identify you to the extent allowed by law.

You will need to provide your social security number. This is in order for you to be compensated for your time. If you do not provide this number, you will not be compensated. If you earn $600 or more by participating in any research, it is potentially reportable for tax purposes.

Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be personally identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. The funding source of this study is the Massage Therapy Foundation, and they may request to look at or copy records that identify you.

In certain circumstances however, you should know that we may be required by law to disclose your information to a court of law. For example, the law may require us to show your information to a court or to tell authorities if you report information about a child being abused or if you pose a danger to yourself or someone else.

Additionally, officials of the University of Kentucky may look at or copy pertinent portions of records that identify you.

CAN YOUR TAKING PART IN THE STUDY END EARLY?

If you decide to take part in the study, you still have the right to decide at any lime that you no longer want to continue. You will not be treated differently if you decide to stop taking part in the study.

The individuals conducting the study may need to withdraw you from the study if you no longer meet the criteria necessary for participation. Should this happen you will no longer be asked to participate. This may occur if you are not able to follow the directions they give you or if they find that your being in the study is more risk than benefit to you.

ARE YOU PARTICIPATING OR CAN YOU PARTICIPATE IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may take part in this study if you are currently involved in another research study as long as there are no medications or physical activity as part of the protocol that would affect the outcome of this study. It is important to let the investigator know If you are in another research study. You should also discuss with the investigator before you agree to participate in another research study while you are enrolled in this study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that is due to the study, please contact the study's medical supervisor. The medical supervisor for this study is Phillip Kern, M.D. Dr. Kern can be reached at (859) 323-4933 OR (859) 323-3775. It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. The medical costs related to your care and treatment because of research related harm will be your responsibility. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study. You do not give up your legal rights by signing this form.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

Upon completion of the study, you will receive compensation based on which group you are randomly assigned to. You will receive $15 for the blood draws and $50 per biopsy. Those assigned to the immobilization group will receive $100. You will receive a $65 bonus for completion of the study. Thus, completion of the study will result in a payment of $375 for the immobilization groups and $130-$180 for weight bearing control groups.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS, CONCERNS, OR COMPLAINTS?

Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions, suggestions, concerns, or complaints about the study, you can contact the investigator, Esther Dupont-Versteegden, Ph.D, at 859-608-0060. If you have any questions about your rights as a volunteer in this research, contact the staff in the Office of Research Integrity at the University of Kentucky at 859-257-9428 or toll free at 1-866-400-9428. We will give you a signed copy of this consent form to take with you.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

If the researcher learns of new information in regards to this study, and it might change your willingness to stay in this study, the information will be provided to you. You may be asked to sign a new informed consent form if the information is provided to you after you have joined the study.

POTENTIAL FUTURE USE

Contacting Research Subjects for Future Studies

Do you give your permission to be contacted in the future by Esther Dupont-Versteegden, Ph.D, regarding your willingness to participate in future research studies about how to prevent, detect, or treat muscle atrophy?

☐ **Yes** ☐ **No** **Initials**

WHAT ELSE DO YOU NEED TO KNOW?

There is a possibility that the data/tissue/specimens/blood collected from you may be shared with other investigators in the future. If that is the case the data/tissue/specimen/blood will not contain information that can identify you unless you give your consent/authorization or the UK Institutional Review Board (IRB) approves the research. The IRB is a committee that reviews ethical issues, according to federal, state and local regulations on research with human subjects, to make sure the study complies with these before approval of a research study is issued.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

Your health information that may be accessed, used and/or released includes:

- Demographic information
- Results of blood tests after ingestion of heavy water
- Analysis of muscle biopsies
- Social Security Number

The Researchers may use and share your health information with:

(*Note: The information listed in this section should include all the agencies/researchers included in the consent form; however, the authorization may require additional information or more specific information than the consent form.)*

- The University of Kentucky's Institutional Review Board/Office of Research Integrity.
- Law enforcement agencies when required by law.
- University of Kentucky representatives.
- The Massage Therapy Foundation
- Center for Clinical and Translational Science (CCTS)

The researchers agree to only share your health information with the people listed in this document.

Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign the form, it will not affect your:

- **Current or future healthcare at the University of Kentucky**
- **Current or future payments to the University of Kentucky**
- **Ability to enroll in any health plans (if applicable)**
- **Eligibility for benefits (if applicable)**

After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:

- You will send a written letter to: Esther Dupont-Versteegden to inform *(him/her)* of your decision.
  900 S. Limestone, CTW Room 204L, Lexington KY 40536-0200
- Researchers may use and release your health information **already** collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).

The use and sharing of your information has no time limit.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Mon-Fri at: (859) 323-1184.

You are the subject or are authorized to act on behalf of the subject. You have read this information, and you will receive a copy of this form after it is signed.

_____ _____
Signature of research subject Date

_____
Printed name of research subject

_____ _____
Name of [authorized] person obtaining informed consent/HIPAA authorization Date

_____
Signature of Principal Investigator or Sub/Co-Investigator