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GRAND FORKS HUMAN NUTRITION RESEARCH CENTER
CONSENT TO PARTICIPATE IN RESEARCH

Project Title: Exercise for Better Bones – Day or Night?
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Department: USDA Grand Forks Human Nutrition Research Center (GFHNRC)

SUMMARY

The purpose of this study is to find out if moderate exercise in the early morning vs evening affects bone health differently in normal to overweight postmenopausal women. You will perform moderate treadmill exercise prescribed by USDA researchers for about half an hour per day, five days per week for 2 weeks in the early morning or in the early evening. You will change to the other time frame for exercise after a 4-6-week break. We will provide all food for three weeks (2 weeks during the study plus one week right before the study). We expect that your taking part in this research will last at least 11 weeks. You may qualify for the study if you are a healthy, postmenopausal woman, willing to maintain usual lifestyle and activities during the study, and willing to perform prescribed moderate intensity exercise. The most important risks or discomforts that you may expect from taking part in this research are blood draws and stool collections.

What should I know about this research?

- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether you participate is up to you.
- If you do not take part, it will not be held against you.
- You can take part now and later drop out if you wish, and it will not be held against you.
- If you do not understand any part of the research or this document, ask questions.
- Ask all the questions you want before you decide.

How long will I be in this research?

We expect that your taking part in this research will last at least 11 weeks including a break period of 4-6 weeks between the 2 exercise treatments. The first information meeting will take about 30 minutes. A screening visit will be scheduled if you agree to join the study. Screening for the study (including a blood draw) should not take more than 30 minutes.

Why is this research being done?

We know that people have biological rhythms with the change of day and night cycle. These rhythms affect short- and long-term physical performance. The purpose of this study is to find out if moderate exercise at different time during the day (early morning vs early evening) affects bone health and calcium use differently in normal to overweight postmenopausal women.

What happens to me if I agree to take part in this research?
If you decide to take part in this research study, you will sign this consent. You will fill out a form which will be used to describe the group characteristics. A W-9 is required before payment can be made. A health history form will help to see if you qualify. You will complete a short physical activity questionnaire.

Inclusion Criteria:

- Postmenopausal women within 1-10 years after menopause and no older than 65 years of age
- BMI 18.5-29.9 kg/m^2.
- Healthy as determined by a screening physical examination and blood chemistry related to thyroid, liver, kidney, and lipid profile within normal range.
- No osteoporosis as determined by DEXA scan at femoral neck or total spinal region.
- No regular exercise for more than 30 minutes a day on more than 2 days a week and no physically active employment, such as maintenance and repair or delivery worker.
- No regular use of medications known to interfere with calcium and bone metabolism from 6 weeks prior to the study to the end of study such as medications for heartburn, reflux, H2 blockers, diuretics, etc. such as antacids, Maalox, Pepcid AC, Nexium, Diuril, etc.
- Weight stable (within 5 lbs change) for at least 3 months prior to the start of the study.
- Willing to maintain usual lifestyle and activities including the same wake-sleep schedule (go to sleep between 10:00 PM and midnight with an average 6-8 hours of sleep time).
- Refrain from the use of alcohol and nicotine (for example, cigarettes, cigars, and e-cigarettes) for the length of the study.
- Able and willing to perform moderate intensity exercise without contraindications as determined by the Physical Activity Readiness Questionnaire.
- Willing and able to stop any nutritional supplements including vitamin D supplements and calcium-containing medications (for instance, calcium-carbonate antacids).
- Willing not to use tanning booths during the study including washout period, or not to travel to locations with a tropical climate two weeks prior to the study or during the washout period.

Exclusion Criteria

- Hypertension with resting blood pressure higher than systolic 140 and diastolic 90 mmHg.
- Within past 6 weeks, had nutrition supplements or medications known to affect calcium metabolism and appetite such as Antacids, Megace, antacids, heartburn, reflux, H2 blockers, diuretics, etc.
- Allergy to any food ingredients used in the provided diet.
- Any disorders affecting nutrient absorption or metabolism, such as cystic fibrosis, lactose intolerance, celiac disease, etc.

- Any sleep disorders such as sleep apnea or regular use of an over-the-counter melatonin supplement.
- Diabetes or taking medications known to affect bone such as Actos, Avandia, Invokana, etc.
- Engaged in moderate to vigorous exercise or regular exercise for more than 30 minutes/day on more than 2 days/week within past 6 weeks.
- Repeated non-compliance with completing prescribed exercise sessions.
- Within past 6 weeks, used tanning booths or travel to locations with a tropical climate two weeks prior to the exercise.
- Use of antibiotics (Amoxicillin, doxycycline, etc.), nonsteroidal anti-inflammatory drugs (aspirin, Celebrex, etc.), or probiotics (Lactobacillus, Bifidobacterium) within the past 6 weeks.
- Irritable bowel syndrome, inflammatory bowel disease, or not having a bowel movement three days or longer.

Eligibility will be determined by the study PI based on the Screening Application, Health History Questionnaire, Physical Activity Readiness Questionnaire, DEXA bone scan, Stanford Brief Activity Survey, and blood chemistry measurements from a separately scheduled fasting (10 hours) screening blood draw. You will need to avoid exercise and alcohol for 72 hours before the screening blood draw. The purpose of the screening blood draw is to determine if your blood chemistries are in the normal range and the results will be reviewed by the study physician.

During the study:

Aerobic Fitness Assessment

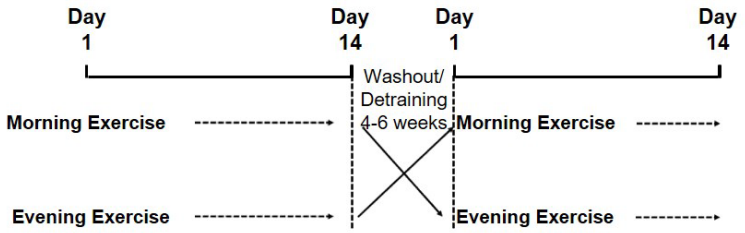
Before the study, you will complete an exercise test to determine the speed and grade setting of the treadmill that will be used during your exercise training sessions. For the graded exercise assessment, you will be fit with a chest strap type heart rate transmitter. Resting heart rate will be recorded at the screening visit after you have sat quietly for 3 minutes. You will complete exercise of increasing intensity until your heart rate reaches at least 150 beats per minute (bpm). After that, you will be walking at speed of 1.8 to 2.5 mph for a cooldown until the heart rate is 120 bpm or less. We will stop the test either at 150 bpm or earlier if you signal that you no longer wish to continue the exercise test.

Exercise Training:

At the beginning, we will assign you either early morning or evening moderate treadmill exercise frame. You will not be able to choose the schedule you want. The exercise training sessions will be completed at the intensity as determined above with the aerobic fitness assessment. We will monitor your heart rate during exercise and make necessary adjustments to the grade of the treadmill. There will be a 3-minute warm-up (1 minute at 2 mph and 2 minutes at 2.5 mph) and a 3-minute cool-down before and after the exercise training. We will record the heart rate and an overall rating of perceived exertion every 5-10 minutes during the exercise training sessions.

After 2 weeks, there will be a 4-6-week break. During the break, you will return to your usual lifestyle like before joining in the study, maintain a stable body weight (within 5 lbs change), and continue the same sleep pattern. If you complete the morning exercise in the first period, you will complete the same exercise in the evening after the break as described below, and vice versa (**Fig 1**).

Fig 1. Study design



Experimental procedures and visits

Morning exercise

Day 2-3 before exercise training

You will come to the GFHNRC for a baseline test to have 2 blood draws (at early morning around 6:30 AM and noon), a 24-hour urine collection, a stool collection, and an Aerobic Fitness assessment (as described above).

Day 1

You will come the GFHNRC at 6:30 AM for a pre-exercise blood draw. At 7:00 AM you will complete a 30-minute treadmill exercise. There will be blood draws at 1 and 2 hours after exercise ends. A 24-hour urine collection will begin after the last blood draw. After the last blood draw at 2-hour, you will be provided your meals for the day (you can eat your meal elsewhere) and released to go home with supplies to continue 24-hour urine collection.

Day 2

You will return to the GFHNRC to return 24-hour urine collection and for a blood draw at 6:30 AM morning and a blood draw at 12:00 noon (before lunch). You will complete a 30-minute treadmill exercise after the morning blood draw.

Day 3-13 (except weekends)

You will come to the GFHNRC between 6:30-7:30 AM to complete the 30-minutes treadmill exercise.

Day 14

The exercise and test procedure will be the same as Day 1.

Evening exercise
Day 2-3 before exercise training
The visit and tests are the same as for the morning exercise period as described above.

Day 1
You will come to the GFHNRC at 5:30 PM for a pre-exercise blood draw. At 6:00 PM you will complete a 30-minute the treadmill exercise. There will be blood draws at 1 and 2 hours after exercise ends. A 24-hour urine collection will begin after the last blood draw. After the last blood draw at 2-hour, you will be provided your dinner meal and you can eat your meal elsewhere. You will be released to go home with supplies to continue 24-hour urine collection.

Day 2
You will come to the GFHNRC for blood draws at 6:30 AM morning and 12:00 noon (before lunch), complete a 30-minute treadmill exercise at 6:00 PM, and return 24-hour urine collection around 8:30 PM.

Day 3-13 (except weekends)
You will come to the GFHNRC between 6:00-7:00 PM to complete the 30-minutes treadmill exercise.

Day 14
The exercise and test procedure will be the same as Day 1.

For all participants, one fresh stool will be collected before the study and at the end of each exercise training.

Diet
Please let us know if you have any food allergies. You will be eating foods we provide to you starting from **one week** before and during the study, except the break period. Foods will be a 5-day rotating menu designed by our Registered Dieticians.

Because fasting and the timing of food intake affect bone markers, you will need to consume the breakfast or dinner within 30 minutes after the exercise on test days (Days 1 and 14) or at standardized times (7:30-8:30 AM, 12-1 PM, 7-8 PM for breakfast, lunch, dinner, respectively) on other days including the weekend during the study.

Sleep and activity monitoring
You will complete the Pittsburgh Sleep Quality Index Questionnaire at the beginning and the end of each phase of the study to assess sleep quality.

We will provide an ActiGraph monitor for you to wear on your non-dominant wrist using a strap. You will wear the monitor starting from 7 days before each exercise treatment period until the end of the study. You will wear the monitor during all awake (except bathing) and sleeping hours for us to monitor physical activity and sleep pattern.

Other
You will complete a brief daily compliance questionnaire with the study diet, mealtime, physical activity, and sleep.

Could being in this research hurt me?
The most important risks or discomforts that you may expect from taking part in this research are:

Exercise: Exercise is generally considered safe and beneficial for individuals without cardiovascular disease (CVD). Given that the recruited participants are healthy with no known underline diseases including no history of CVD and perform only moderate exercise (60% heart rate reserve), it is unlikely they will have a serious CVD event or other exercise related injuries. However, there is always risk of falls, lightheadedness, and feeling faint. Additional safeguards include monitoring of heart rate and rating of perceived exertion every 5-10 minutes during exercise, 3-minute warm-up (1 minute at 2 mph and 2 minutes at 2.5 mph at 0% grade), and 3-minutes of cool-down (in reverse order as warm-up). For non-exercise trained peri-menopausal women during aerobic fitness assessment, 60% heart rate reserve should occur at approximately 130-140 beats/min so the fitness testing at 150 beats/minute will allow us to determine the training workload while avoiding the risks of exercise test.

Blood Draws: The risks associated with blood sampling are small and usually limited to local bruising or swelling. Volunteers may sometime feel lightheaded or faint during or right after a blood draw, and in very rare cases experience a seizure during or right after a blood draw. If you have had problems with fainting during blood draws in the past, you may be more prone to them during future procedures. Trained staff will use sterile techniques when drawing blood. However, there is a slight chance that the site may become infected. A maximum of 292 milliliters (about 20 tablespoons or 1 ¼ cup) will be drawn over the entire study. This value is much less than the pint or 475 milliliters that blood banks may draw every 8 weeks.

DEXA scan: The scan is an x-ray and considered to be a no greater than minimal risk procedure. The radiation dose of the whole-body scan is no more than 1.0 millirem. This dose is equal to roughly 1/620 of normal annual background radiation, 1/4 of the radiation received in a long flight, or 1/10 of the radiation received in a chest x-ray. A quality assurance check will be completed on the DEXA each day prior to its use; the software will not allow the use of the DEXA if the quality assurance check fails. Each subject will receive 1 DEXA scan, and an extra scan may be needed.

Stool collection: There are no risks associated with a stool collection. However, some people may feel unconfortable in the collection procedure.

Questionnaires: You may feel uncomfortable answering some of the survey questions. Only questions required to determine eligibility and to assess factors related to the research will be asked. If there is a question(s) you wish to not answer, please inform the staff.

Will being in this research benefit me?
Although you may not benefit personally from being in this study, we hope that, in the future, others might benefit from our findings. Results of the research may yield knowledge of how the daily timing of exercise affects bone health. This may provide important information that may guide exercise advice to improve bone health in postmenopausal women.

How many people will participate in this research?
Approximately 25 people will take part in this study at the Grand Forks Human Nutrition Research Center.

Will it cost me money to take part in this research?
You will not have any costs for being in this research study. You will be expected to provide your transportation to and from the GFHNRC. We do not withhold income, social security, unemployment taxes, or any other taxes because you are not an employee of the GFHNRC. You may have to pay income taxes on the money you receive. All tax questions regarding the taxability of the payment should be directed to your personal tax accountant or to your local Internal Revenue Service Office. If you are not a United States citizen, check your documentation to make sure you can receive money from a non-University source without risking your status in the United States.

Will I be paid for taking part in this research?
You will be paid for being in this research study. Reimbursement for completing the study is $1,710, OR a 39-month individual membership, OR a 28-month family membership to the Choice Health & Fitness. If you have had a blood draw as part of screening but are found ineligible, you will be paid $25. If you decide to drop out of the study, you will be paid a prorated amount for the procedures completed. If you complete the entire study, payment will be made following completion.

Who is funding this research?
The United States Department of Agriculture (USDA) is funding this research study. This means that the GFHNRC is receiving payments from the USDA to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or an increase in salary from the USDA for conducting this study.

What happens to information collected for this research?
Your private information may be shared with individuals and organizations that conduct or watch over this research, including:

- The GFHNRC
- The USDA, as specified in the USDA/ARS Privacy Act System of Records
- The University of North Dakota (UND) Research Compliance & Ethics Office
- The Institutional Review Board (IRB) that reviewed this research
- The study supervising physician at the UND School of Medicine and Health Sciences
- As required by law or court order.

We may publish the results of this research. However, we will keep your name and other identifying information confidential. We protect your information from disclosure to others to the extent required by law. We cannot promise complete secrecy. Clinical trial information will be submitted to the National Institutes of Health/National Library of Medicine to be included in the clinical trial registry data bank (www.clinicaltrials.gov).

Data or specimens collected in this research will be de-identified and might be used for future research or distributed to another investigator for future research without your consent.

Could being in this research hurt me?
In the event that this research activity results in an injury, treatment will be available including first aid, emergency treatment and follow-up care as needed. Payment for any such treatment is to be provided by you (you will be billed) or your third-party payer, if any (such as health insurance, Medicare, etc.) No funds have been set aside to compensate you in the event of injury. Also, the study staff cannot be responsible if you knowingly and willingly disregard the directions they give you. If you are injured while taking part in this research project as a result of the negligence of a United States Government employee who is involved in this research project, you may be able to be compensated for your injury in accordance with the requirements of the Federal Tort Claims Act. Compensation from individuals or organizations other than the United States might also be available to you.

What if I agree to be in the research and then change my mind?
If you decide to leave the study early, we ask that you inform the study coordinator or the principal investigator, Jay Cao at 701-795-8377 (jay.cao@usda.gov).

Your decision will not affect your current or future relations with the GFHNRC or UND.

If you begin taking medications during the treatment period, please let study staff or the investigator know. Some medications may interfere with the outcomes of the study. If your medications interfere with the study outcomes, your participation will be ended, and you will be compensated for the portions of the research completed.

Approval Date: 5/3/2024

Expiration Date: 5/2/2025

University of North Dakota IRB

Date: _____
Subject Initials: _____

Who can answer my questions about this research?
If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page.

This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. You may talk to them at 701.777.4279 or UND.irb@UND.edu if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.
- You may also visit the UND IRB website for more information about being a research subject: http://und.edu/research/resources/human-subjects/research-participants.html

Request to contact for future studies:
We would like to alert you about studies you may qualify for in the future. Please indicate below if you consent to be contacted.

(Please circle one) YES NO Initials _____

Consent:
Your signature documents your consent to take part in this study. You will receive a copy of this form.

Subject's Name: _____

_____ _____
Signature of Subject Date

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative.

_____ _____
Signature of Person Who Obtained Consent Date

Approval Date: 5/3/2024

Expiration Date: 5/2/2025

University of North Dakota IRB

Date: _____
Subject Initials: _____