The influence of irisin/FNDC5 on bone mineral density and fracture risk in individuals with spinal cord injury

NCT05319522

November 8, 2024

Subject Name: _____Last 4 SSN:_____ Date: _____

Title of Study: Irisin/FNDC5 in individuals with spinal cord injury and its association with bone health

Principal Investigator: XXXXXXXXXX VAMC: Pittsburgh (646)

LAY TITLE: The relationship between irisin and bone health in individuals with spinal cord injury

KEY ELEMENTS: This is a research study to determine if a protein called irisin, which is released by muscle into circulation, is related to the density and strength of lower limb bones in people with spinal cord injuries. Additionally, this research study seeks to determine if high-intensity upper body exercise can be used to increase the amounts of this protein in circulation. Your participation in this study is voluntary.

You will complete two testing visits, one at the University of Pittsburgh Neuromuscular Research Laboratory and a second visit at the VA Pittsburgh Healthcare System Research Office Building. At visit one, you will complete questionnaires related to your demographics, health history, wheelchair use (if applicable) and physical activity, two different bone scans and an upper body graded exercise test. At visit two, you will complete a resting blood draw and upper leg muscle biopsy, a high intensity upper body exercise bout and a post-exercise blood draw. The first clinic visit will take approximately 3 hours and the second visit will take approximately two hours. We aim to complete both visits within a two-week period.

There are risks to this study that are described in this document. Some risks include: muscle soreness and fatigue from the exercise, infection, bruising, bleeding and fainting from the blood draws and biopsy and radiation risks from bone scans You will not directly benefit from participating in this study. You may however, receive indirect benefit given that you are contributing to medical science or helping to advance future understanding of the role of muscle released proteins on bone health. This research could lead to more effective rehabilitation strategies to reduce or reverse bone loss for people with spinal cord injuries

If you do not participate in this study, alternate treatments for spinal cord injury associated bone loss include: antiresorptive medication, mechanical loading, and functional electrical stimulation exercise.

If you are interested in learning more about this study, please continue reading below.

STUDY CONTACT INFORMATION:

Subject Name: _____Last 4 SSN:_____ Date: _____

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Principal Investigator: XXXXXXXXXX VAMC: Pittsburgh (646)

If you have a general question about this research study, or if you have any concerns or complaints related to this research study, you may call any of the investigators listed below.
If you experience any illness, injury or other medical problem that you feel may be related to this study, please call XXXXXXXXXX at XXXXXXXXXX and after-hours or on weekends call 1-866-785-9015 and tell the operator that you are a research subject from the Pittsburgh VA in "Irisin/ FNDC5 in individuals with spinal cord injury and its association with bone health" study and need to speak with XXXXXXXXXX. Then give the operator a phone number where you can be reached. The operator will get in touch with XXXXXXXXXX or another person listed below who will call you back.

XXXXXXXXX
Principal Investigator.
Telephone: XXXXXXXXX
Address: XXXXXXXXXX

XXXXXXXXXX
Co-Investigator
Telephone: XXXXXXXXXX
Address: XXXXXXXXXX

XXXXXXXXXX
Co-Investigator
Telephone: XXXXXXXXXX
Address: XXXXXXXXXX

STUDY SPONSOR:
VA Rehabilitation Research and Development Service – Career Development Award

Additional information regarding the study sponsor can be provided upon request.

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PURPOSE OF THE RESEARCH STUDY: The purpose of this research study is to determine if a protein called irisin, which is released by muscle into circulation, is positively related to bone health and can be used to improve rehabilitation strategies to slow or reverse bone loss following spinal cord injury. This research study has multiple aims. The first aim is to determine if irisin levels in the blood are related to the density and strength of lower limb bones in people with spinal cord injuries. The second aim is to determine if irisin levels in the blood differ between people with and without spinal cord injuries due to changes that occur in the muscle following injury. Lastly, this research study seeks to determine if high-intensity upper body exercise can be used to increase the amounts of this protein in circulation. These different aims will help determine if increasing irisin levels in the blood through upper body exercise can help improve the effectiveness of rehabilitation treatments to slow or reverse bone loss.

You are being asked to participate in this research study because you are a Veteran or non-Veterans with a traumatic spinal cord injury that occurred at least 12 months ago and use a manual wheelchair for 30 or more hours per week. Alternatively, you are a healthy Veteran that is of a similar age and sex to a participant with spinal cord injury. We aim to complete 22 participants with spinal cord injury and 22 age and sex matched control participants

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at any time.

DESCRIPTION OF THE RESEARCH STUDY:
You will complete testing visits at the University of Pittsburgh Neuromuscular Research Laboratory and the VA Pittsburgh Healthcare System Research Office Building. At visit one (Neuromuscular Research Laboratory), you will complete questionnaires related to your demographics, health history, wheelchair use (if applicable) and physical activity, bones scans of your lower leg and whole body, and an upper body graded exercise test. At visit two (VA Research Office Building), you will complete a resting blood draw and upper leg muscle biopsy, a high intensity upper body exercise bout and a post-exercise blood draw.

Visit 1:

a) Pregnancy Test: Pregnant women will be excluded from participation in this study due to the use of ionizing radiation by the two bone imaging devices and the unknown consequences of ionizing radiation to a fetus. Females who decide to participate in the study will be asked to complete a pregnancy test prior to any further data collection. A positive pregnancy test will result in removal from the study by the study team.
b) Questionnaires: You will complete two questionnaires which will require approximately 20-30 minutes. The first questionnaire includes demographic information such as age, race and asks general health and medical history questions. For participants with spinal cord injury, this questionnaire also asks questions about wheelchair use. The second questionnaire evaluates physical activity levels.
c) Bone Scans: You will complete a whole body DXA scan which measures bone mineral density as well as body composition. You will be required to wear clothing without zippers or buttons (athletic clothing) and must lay still on a flat table with minimal movement and normal breathing for approximately 20 minutes. During this time, a small mechanical arm will pass over your body taking images of the bone, tissue, and fat. The second bone scan, the HR-pQCT will scan two areas of your lower leg. You will be placed in a chair, with your non-dominant foot propped up, and placed in a removable cast boot to keep it from moving. You will be asked to keep your lower extremities as still as possible during the course of the scan, which will last approximately 3 minutes.
d) Maximal Exercise Testing: At the first visit, you will complete a stationary, upper body aerobic capacity test using an arm ergometer (hand cycle). During the test, work rate (the speed at which you operate the hand cycle) will increase incrementally every minute until you are no longer able to meet the required speed or choose to stop. You will be verbally and visually cued to maintain a set speed. Your oxygen consumption (VO2) will be measured continuously throughout the test, which will end when you can no longer maintain the prescribed speed. From this test, we will determine your peak power output (the highest amount of power achieved during the test), which we will use to set the intensity for your high intensity interval exercise bout at the second visit.

Visit 2:

a) High intensity interval exercise bout: At the second visit, you will perform a high-intensity interval exercise bout on the arm ergometer with the intensity based off your peak power output.

Following a three-minute warm up, you will perform ten intervals with 1:1 minute work/recovery phases followed by a 2-3 minute cooldown.

b) Blood draws: You will be asked to relax your arm, palm side up, on an arm rest, as certified personnel collect samples in the crease of your arm. This is no different than if you were to give blood as a donation or for testing in a doctor's office. Blood will be drawn before and after the exercise bout at the second testing visit. Each blood draw will be less than 1 tablespoon of blood

c) Muscle biopsy: A single muscle biopsy will be collected from the outer portion of your quadriceps (thigh) muscle. After the biopsy site is sterilized, lidocaine (numbing medication) will be injected. After the numbing effect takes place, a scalpel will be used to make a small incision, a few millimeters, and a small needle will be placed into the thigh, removing a small sample of the muscle, about the size of 1/4 of a pea. The wound will be closed with steri-strips dressed, and you will be monitored for proper care. We will provide you with post-procedure care instructions for the biopsy site. We will speak with you via telephone 48-72 hours following the biopsy to ensure that the wound is healing correctly.

Testing visits one and two will take approximately three and two hours to complete, respectively. We will aim to complete all both testing visits within a period of two weeks.

During these tests we may see something that should be checked by your primary care doctor. If that happens, we will call you within a week of the test to let you know. We will then send the test results to your primary care doctor. If you are a veteran and do not have a primary care doctor, we will refer you to one within the VA system. Please note that we are not specifically looking for any medical problems so it is very unlikely that we will find any underlying issues. This test is not the same as regular medical care.

Blood samples will be collected at the second testing visit, before and after the upper body exercise bout. A muscle biopsy will also be collected from your upper leg muscle before the exercise bout. The bone scans will be used to measure bone density, size, shape, structure and strength. The whole-body scan will also be used to measure your body composition. The performance data that we collect in the graded exercise test in visit one will be used to determine the intensity of the exercise bout at visit two. All data and biological specimens will be labeled solely with your subject number (and timepoint for the blood samples). The biological specimens will be stored until they have been analyzed and the resulting data has been published. After the data that results from these biological specimens has been published, any

remaining specimens will be destroyed. Paper data records will be stored for six years from the fiscal year end in which the study was completed.

RISKS AND BENEFITS:

Muscle Biopsy: The risks of a muscle biopsy include pain, fainting, bruising, infection, bleeding, muscle soreness, scarring, possible temporary muscle damage such as lack of ability to generate force, numbness or weakness. The pain experienced from a muscle biopsy may be slight or may be more severe, as it varies person to person. The risks of using lidocaine are pain and tingling at time of administration, temporary burning feeling, bruising; temporary effects include: loss of local feeling, blurred vision, dizziness, vomiting, headache, muscle twitch, and weakness.

Graded Exercise Test and High Intensity Interval Exercise: Muscle soreness is a common risk associated with novel, high intensity exercise. This soreness typically develops 2-3 day after the fatiguing protocol and will last approximately 2-3 days. There is also an infrequent risk of death or heart attack during or following a maximal exercise test. According to the American College of Sports Medicine, the risk associated with maximal physical fitness testing is considered relatively low in young, healthy adults. The risk of a complication requiring hospitalization is less than or equal to 0.2% and the risk of death during or immediately after an exercise test is less than or equal to 0.1%.

Bone Scans: Participation in this research study involves exposure to radiation from x-rays. The amount of radiation exposure that you will receive from this procedure(s) is equivalent to a uniform whole-body dose of less than 1 mSv (a “mSv” is a unit of radiation dose), which is approximately 2% of the radiation dose (50 mSv) permitted to an occupational radiation worker in one year. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from participation in this study is considered to be low when compared to everyday risks. Because the investigators assume that this study represents the only research exposure to radiation that you will be exposed to, it is important that you inform the investigators of your participation in any other research studies or situations involving X-ray, nuclear medicine scans, or workplace exposure to radiation during the past year.

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Blood Draws: Blood draws involve the use of a needle, which will be inserted into a vein. Therefore, there is a risk of infection, bruising, slight pain, or fainting may occur. Only qualified researchers will complete this test, and thereby minimize any previously mentioned risk. If any medical abnormalities are identified, your results will be sent to the study physician to review and discuss with you. The study physician will refer you for follow-up testing or treatment as necessary.

Participation in this research study may involve unforeseeable risks to you.

Because there may be other risks associated with participating in multiple research studies, you must tell the research staff about any other studies you are currently participating in, both within and outside of the VA."

PREGNANCY RISKS
The safety of ionizing radiation from HR-pQCT and DXA scans during pregnancy is not known. If you are pregnant, you cannot take part in this study. Urine pregnancy tests will be done at the initial visit and during the study.

Biological specimens will be stored in a freezer at the University of Pittsburgh Neuromuscular Research Laboratory until all data have been analyzed and published. The risk of a breach of privacy and confidentiality is minimal as all biological specimens will be labeled using only your subject number and the sample time point, if applicable.

You will not directly benefit from participating in this study. You may receive indirect benefit given that you are contributing to medical science or helping to advance future understanding of the role of muscle released proteins on bone health. This research could lead to more effective rehabilitation strategies to reduce or reverse bone loss for people with spinal cord injuries.

Study participants will not receive any direct benefit from providing biological specimens. There are no commercial benefits to these findings.

ALTERNATIVES TO PARTICIPATION:

There may be other studies that you qualify for. Talk to your provider about such options. You have the alternative to not participate in this research study

NEW FINDINGS: You will be informed of any significant new findings during the course of the study, which may affect your willingness to continue to participate. Individual research results will not be returned to you.

INVESTIGATOR INITIATED WITHDRAWAL: The investigator(s) may stop your participation in this study without your consent for reasons such as: it will be in your best interest; you do not follow the study plan; or you experience a study-related injury.

VOLUNTARY PARTICIPATION/RIGHT TO WITHDRAW: Your participation in this study is voluntary. You do not have to take part in this study, and your refusal to participate will involve no penalty or loss of rights to which you are entitled. You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled.

If you choose to withdraw from the study, please notify the principal investigator, XXXXXXXXXX, in writing or by telephone call XXXXXXXXXX. If you are withdrawn from the study team you will be notified in person or by phone call by the principal investigator. If you withdraw or are withdrawn from the study following the muscle biopsy procedure, you are still entitled to have the biopsy site inspected by the research team to ensure that it is healing properly.

If you withdraw or are withdrawn from the study, your data and biospecimens may still be used for analysis by the research team at their discretion, unless you specifically withdraw your consent to use your data. If you withdraw your consent for the research team to use any collected data, please express this request in an email to the principal investigator.

If you withdraw your consent and authorization for such use, you may not be able to continue to participate in the research study.

MEDICAL TREATMENT: In the event that you sustain injury or illness as a result of your participation in this VA approved research study, conducted under the supervision of one or more VA employees, all

medical treatment (emergent as well as medical treatment beyond necessary emergent care) will be provided by the VA. Except in limited circumstances, the necessary medical care must be provided in VA medical facilities.

However, if such injury or illness occurred as a result of your failure to follow the instructions for this study, you may not be eligible for free care unless you have independent eligibility for such care under Federal Law.

FINANCIAL COMPENSATION: If you sustain an injury or illness as a result of participating in this research study, you may be eligible to receive monetary compensation for your damages pursuant to applicable Federal law. If you believe that you are injured as a result of participation in this study, please contact the Principal Investigator. If compensation is available the Principal Investigator will provide you with an explanation as to what that compensation consists of, or where you can obtain further information regarding it.

COST AND PAYMENTS: You or your insurance will not be charged for any costs related to the research. However, if you are receiving medical care and services from the VA that are not part of this study, and you are a veteran described in Federal regulations as a "category 7" veteran, you may be required to make co-payments for the care and services that are not required as part of this research study. Participants with SCI will receive $40 for completing testing visit one and $80 for completing testing visit two for a total of $120. Control participants will receive $25 for completing testing visit one and $55 for completing testing visit two for a total of $80. Except in limited circumstances, payments issued through VA are generated by Electronic Funds Transfer (EFT). Therefore, in order to receive payment associated with your participation in this study, you must be willing to receive EFT and to provide banking information to VA, if that information has not already been provided. If you are not able to receive payment through EFT, the Direct Express Debit MasterCard may be issued. The Direct Express Debit MasterCard is a prepaid debit card. Please refer to the flyer that study personnel has provided for more information about which services may require a fee if using your Direct Express Debit MasterCard. In addition, due to limitations in the Financial Management System, payments made to you will generate Internal Revenue Service (IRS) Form 1099 regardless of amount. Payments will be reported to the IRS as income and your social security number will be used for this purpose.

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RECORD RETENTION: Your research records will be retained in accordance with the Veterans Health Administration (VHA) Records Control Schedule, or longer, if required by other Federal regulations.

CONFIDENTIALITY AND USE AND DISCLOSURE OF DATA: There are rules to protect your private health information. Federal and State laws and the Federal medical law, known as the HIPAA Privacy Rule, also protect your privacy. By signing this form, you provide your permission called your 'authorization', for the use and disclosure of information protected by the HIPAA Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including:

Demographic Information such as name, age, race, date of birth
Questionnaire data regarding physical activity, medication use, injury history
Two blood samples
A muscle biopsy
Whole body bone mineral density and body composition
Lower leg bone density, geometry (e.g. circumference, area) and microarchitecture (e.g. trabecular number, trabecular spacing, cortical porosity)

The research team may also need to disclose your health information and the information it collects to others as part of the study progress. Others may include the:

The University of Pittsburgh Institutional Review Board who will monitor the study
The VA Rehabilitation Research and Development Service who is funding this study

While this study is being conducted, you will not have access to your research related health records. This will not affect your VA healthcare including your doctor's ability to see your records as part of your normal care and will not affect your right to have access to the research records after the study is completed.

A progress note stating you are participating in this study will not be placed within your medical record.

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In addition, Institutional Review Board, Food and Drug Administration, Office (FDA), Office of Human Research Protections (OHRP), the VA Office of Research Oversight (ORO), and the Government Accountability (GAO) may have access to your research records. Your health information disclosed pursuant to this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient. Additionally, any medical information may be shared with your healthcare provider(s) with your consent, and possibly without your consent if permissible under Federal laws and regulations.

Finally, you consent to the publication of the study results or release of the data when published, so long as the information about you is anonymous and/or disguised so that your identity will not be disclosed

Confidentiality risks and precautions to decrease risk:
Every effort will be made to make sure that the information about you obtained from this study will be kept strictly confidential. As private information is collected about you as part of this study, there is a risk to your privacy and confidentiality. The research staff will take every precaution to protect your identity and the confidentiality of the information collected about you.

Any electronic or hard/paper copies of the information collected about you will be stored in a secured location. Only those individuals who are authorized to review your information will have access to it. A portion of blood sample will be processed and transported to the University of Pittsburgh Biomedical Mass Spectrometry Center for analysis of irisin levels. These samples will be labeled only with your subject number and time point (pre- or post-exercise). After analysis by the Biomedical Mass Spectrometry Center, the resulting data will be stored in a secured computer at the Human Engineering Research Laboratories.

Future Use
Your information and biospecimens will not be used or distributed for future research studies.

Revocation: You can revoke this authorization, in writing, at any time. To revoke your authorization, you must write to the Principal Investigator at the address below. Your request will be valid when the Release of Information Office receives it. If you revoke this authorization, you will not be able to

continue to participate in the study. This will not affect your rights as a VHA patient to treatment or benefit outside of the study.

XXXXXXXXXX

Treatment, payment or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization. This authorization will expire at the end of the research study unless revoked prior to that time.

RESEARCH SUBJECTS' RIGHTS: You have read or have had read to you all of the above. XXXXXXXXXX or his authorized representative has explained the study to you and answered all of your questions. The risks, discomforts, and possible benefits of this research study, as well as alternative treatment choices, have been explained to you.

A description of the study has been provided to you, including an explanation of what this study is about, why it is being done, and the procedures involved. You have the right to ask questions related to this study or your participation in this study at any time. You should be giving your consent only under conditions in which you (or the person representing you) have sufficient opportunity to carefully consider whether or not to participate in this study. Your consent should not be given under conditions that pressure you or try to influence your decision in any way.

Your rights as a research subject have been explained to you, and you voluntarily consent to participate in this research study. You will receive a copy of this signed consent form.

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If you have any questions about your rights as a participant in this study, or wish to speak more about the study with someone not associated with the research study, you can call the Associate Chief of Staff for Research and Development at XXXXXXXXXX.

As long as the study is renewed as required by the IRB, your signature on this document is valid for the duration of the entire research study. Should any changes occur during the course of the study that may affect your willingness to participate, you will be notified.

By signing this form, you agree to participate in this research study.

_____	_____	_____
Subject's Signature	Subject (Print)	Date
_____	_____	_____
Investigator/Person Obtaining Consent*	Researcher (Print)	Date

Version Date – October 23, 2024