COVER PAGE

A Double-Blind, Placebo-Controlled Trial of Anti-Aging, Pro-Autophagy Effects of Metformin in Adults with Prediabetes

NCT03309007

5.10.2018

The University of New Mexico Health Sciences Center
Consent to Participate in Research

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Introduction

You are being asked to participate in a research study being conducted by Mark Burge, M.D., from the Department of Internal Medicine, and Vojo Deretic, Ph.D., from the Department Molecular Genetics and Microbiology, who are the Principal Investigators, as well as such assistants as they may require. This is a clinical research study designed to examine the beneficial "pro-autophagy" effects of the diabetes drug Metformin in adults with prediabetes. The term autophagy refers to the process by which your body's cells clean out toxins and debris, and recycles damaged cell parts. Activation of your body's autophagy process may make it possible to reduce inflammation, improve biological function, fight disease, and even slow down the aging process. Dr. Deretic's laboratory has been studying autophagy and the possibility that this process may combat disease states for many years, as well medications that might induce the beneficial effects of autophagy.

The purpose of this study is to determine whether Metformin, a well-known diabetes medication, might have broader health applications beyond the treatment of diabetes. This is a pilot study, which means that we are gathering preliminary information to determine if a larger study is warranted. We hypothesize that, in addition to beneficial effects of Metformin on blood glucose level, body weight, and body composition, Metformin will exert beneficial effects on other measures of inflammation and aging by stimulating the autophagy process. We propose to study such measures by examining Metformin's effects on several separate measures of cellular autophagy.

As part of this research, we will utilize human white blood cells as tools to look at intracellular interactions and the effects of Metformin. For this purpose, we require a moderate amount of blood to be drawn during the course of the study. Your participation in this study will last about 3 months and will include four visits to the UNM HSC Clinical Research Unit several weeks apart.

You are being asked to participate in this study because you are a healthy person between the ages of 30 and 70 years who has been identified as having prediabetes based upon prior blood tests, or because you have risk factors that suggest you are at risk for prediabetes. These risk factors include a family history of type 2 diabetes, a history of gestational diabetes, an elevated body weight, Hispanic ethnicity, or a non-Caucasian race. You may not participate in this study if you have taken any diabetes medication in the past six months or if you are taking steroid medications. You must also be free of serious kidney or liver disease to participate in this study, and if you are a woman of child-bearing age, you must agree to not get pregnant during this study and to use an effective method of birth control during the course of the study. Finally, you may not participate in this study if you have Crohn's Disease or Ulcerative Colitis, or if you have ongoing alcohol or substance abuse.

This form will explain the research study, and will also explain the possible risks and benefits of the study to you.

What will happen if I decide to participate?

If you agree to participate, the following things will happen:

You will have an initial screening visit, at which time you will receive a standard medical history and physical examination, and your medical records and current medication list will be reviewed by study personnel. You will also be asked to complete a short health-history questionnaire and an alcohol use questionnaire. If you are female of child-bearing age, you will receive a urine pregnancy test to ensure that you are not pregnant. You will have blood tests drawn to make sure that you qualify for the study and to determine that your kidney and liver function is normal. It is expected that this visit will take 1 or 2 hours to complete.

If you meet study criteria and elect to participate, you will receive a total of 12 weeks of treatment with either Metformin or a matching Placebo. The treatment you are assigned to will be determined randomly, which is like the flip of a coin. You will also be asked to follow an ADA-recommended diet, and you will be given a step counter and asked to walk 10,000 steps per day 5 days per week for the remainder of the study. The step-counter will be yours to keep. You will also be given a diary in which to record your daily step count. Study medication will need to be taken with a glass of water twice a day: one pill twice a day for 1-4 weeks, then two pills in the morning and one pill in the evening for the remainder of the study.

In this study, the investigators will be blinded to treatment assignment, so neither you nor they will know whether you are receiving Metformin or Placebo treatment until the completion of the study. The study randomization list will be maintained by the UNM Hospital Research Pharmacist, Susan Kunkel, PharmD.

Study visits will occur at the UNM HSC Clinical Research Unit at 0 weeks (baseline), 4 weeks, and 12 weeks. At each visit, approximately 12 teaspoons of blood will be collected to measure your A1c level (a measure of your blood sugar over the past several weeks), your blood sugar, insulin, blood salts, and kidney function. Additionally, blood will be used to determine our measures of autophagy. These tests are called LC3, TFEB, Galectin-3, and DNA Methylation. No specific genetic tests will performed during this study. Your height, weight, and blood pressure will be recorded at every visit, and at week 0 and week 12, you will receive a Bioelectrical Impedance test to measure your body composition (percent lean and percent fat). The Bioelectrical Impedance test runs a small electrical current through your body to measure your percent lean and percent fat. This test is the same as the one currently available on many bathroom scales and is not known to possess any serious risks. Study personnel will also collect your step diary and count how many remaining pills of study medication you have left at each visit.

Below is a Table that outlines the procedures that will occur over the course of the study:

Visit	Screening: 1-2 hour outpatient visit	Week 0; 1-2 hour outpatient visit	Week 4 (± 7 days): 1-2 hour outpatient visit	Week 12 (± 7 days): 2 hour outpatient visit
Event	Sign consent form. Medical history and physical exam, health history questionnaire. Labs for A1c, blood salts, kidney and liver function. Urine pregnancy test (if appropriate)	Height and weight, body composition. Labs for A1c, blood sugar, insulin, fasting glucose, blood salts, kidney function, TFEB, LC3 score, Galectin 3 and DNA Methylation. Study medication & step-counter provided	Height and weight. Labs for A1c, fasting glucose, insulin, blood salts, kidney function, TFEB, LC3 score, Galectin 3 and DNA Methylation. Study medication and step-diary collected.	Height and weight, body composition. Labs for A1c, fasting glucose, insulin, blood salts, kidney function, TFEB, LC3 score, Galectin 3 and DNA Methylation. Study medication and step-diary collected

How long will I be in this study?

Participation in this study will take a total of approximately 6-10 hours over a period of 12 weeks, and 4 visits to the UNM HSC Clinical Research Unit will be required (including the initial screening visit).

What are the risks or side effects of being in this study?

Study medication risks: You may experience some side effects from the study medication. Approximately 20% of patients experience gastrointestinal bloating with Metformin, but these symptoms tend to improve over time. Some of the more common side effects of metformin include abdominal or stomach discomfort, cough or hoarseness, decreased appetite, diarrhea, fast or shallow breathing, fevers or chills, a general feeling of discomfort, lower back or side pain, muscle pain or cramping, painful or difficult urination, and sleepiness. Less common side effects of metformin include anxiety, blurred vision, chest discomfort, cold sweats, coma, confusion, cool or pale skin, depression, difficult or labored breathing, dizziness, fast or irregular or pounding or racing heartbeat, a feeling of warmth, headache, increased hunger, increased sweating, nausea, nervousness, redness of the face or neck or arms or upper chest, seizures, shortness of breath, slurred speech, tightness in the chest, unusual tiredness or weakness, or wheezing. Rare side effects of metformin include a behavior change similar to being drunk, difficulty with concentration, drowsiness, lack or loss of strength, or restless sleep.

The medication that we are using as a Placebo in this study is Calcium Carbonate ($CaCO_3$). Calcium carbonate is a dietary supplement that is used to provide extra calcium when the amount of calcium in a person's diet is insufficient, and it is also used to prevent the development of osteoporosis (weak bones) in older adults. Calcium is needed by your body for healthy bones, muscles, nervous system, and heart. Calcium carbonate also is used as an antacid to relieve heartburn, acid indigestion, and upset stomach. It is available with or without a prescription. In this study, you may be asked to take a preparation that includes calcium carbonate at a dose that is consistent with current treatment recommendations. Calcium is generally recommended for healthy adults in doses of up 1000 mg per day in adults, and in this study, you might receive 780 mg daily if you are assigned to the placebo group. You should not take other calcium supplements while you are participating in this study.

The side effects of Calcium Carbonate therapy include a small risk of kidney stones (< 1%), and gas, bloating or constipation in up to 30% of patients. Calcium Carbonate CO3 may also interfere with the absorption of certain other drugs from your gut. These medications include certain antibiotics (quinolones, tetracyclines), certain osteoporosis medications (alendronate, residronate), heart and blood pressure medications (digoxin, diltiazem, verapamil, amlodipine), thyroid hormone (levothyroxine), and diuretics (hydrochlorothiazide). Additionally, estrogen therapy might increase the absorption of Calcium from your gut. For the most part, these effects can be avoided by taking the study medication at least an hour before or after your other medications. If you have any concerns that calcium carbonate therapy is not right for you, you should check with your healthcare provider prior to enrolling in this study. You should report any

side effects you experience while taking part in this study to your study doctor and to study personnel.

Blood drawing risks: Drawing blood with a needle may cause temporary pain and discomfort from the needle stick. Bruising at the site of the needle insertion, sweating, feeling faint or lightheaded and, in rare cases, skin infection may also occur. There is also a less than 1% chance of passing out briefly during the blood draws. If this occurs, you will be sked to lie down and rest until you feel better. All blood draws will occur in a clinic setting and will be performed by a phlebotomist who is trained in aseptic technique and in recognizing the signs of distress. After the blood draw, you will be provided a bandage and wound care instructions. In the event that you feel faint or shaky after the blood draw, you may be provided with a small snack.

According to current medical study guidelines, you should not donate too much blood at one time. The total amount of blood to be obtained during this 12-week study is less than ½ of a typical blood donation. If you are a blood donor, you should plan not to donate blood until more than 8 weeks after the completion of the study.

Allergic reaction: Although allergies to Metformin are rare, there is a risk of allergic reaction with any drug. Symptoms of an allergic reaction may include, but are not limited to, trouble breathing, fast heart rate, rash, dizziness, itching, and swelling. If you experience any of these symptoms, you should contact the study team immediately or present to the nearest emergency room.

Bioelectrical Impedance Analysis: This procedure may cause mild skin irritation from electrode adhesives, and/or temporary discomfort, although this is uncommon. We will not perform this test in people with a lot of metal in their body (such as a metal hip or other joint replacement), those with amputations, those who have received radiographic contrast material within the last 72 hours, or people with coronary artery stents or metallic sutures, since these factors can interfere with the test results.

Reproductive Risks: There are no known reproductive risks in this study, and Metformin has been used safely during pregnancy on many occasions. Nevertheless, you may not participate in this study if you are pregnant. If you are a woman of child-bearing age, you should employ an acceptable method of birth control (i.e.- condoms or other barrier method, birth control pills, an IUD, or long-acting implantable contraception) for the duration of the study. Please notify study personnel immediately if you become pregnant during the course of this study.

General: There are risks of stress, emotional distress, inconvenience and possible loss of privacy and confidentiality associated with participating in any research study.

Risks of Stopping Metformin: If you take metformin during this study, you may experience a benefit from it, such as lower blood glucose levels, that will go away after the drug is stopped. If you agree, we can send information about how you did during this study to your primary care provider so that you and he/she can discuss whether or not to continue with metformin treatment.

What are the benefits to being in this study?

Although some people lose a small amount of weight with Metformin therapy, it is possible that there will be no direct benefit to you from participating in this study. However, it is hoped that information gained from this study will help in the future understanding and treatment of prediabetes. Additionally, this study will help us better understand whether or not Metformin might have an anti-aging effect on your body's cells.

What other choices do I have if I do not want to be in this study?

You do not have to participate in this study to receive treatment for your prediabetes. The United States Food and Drug Administration has approved Metformin, as well as other types of medication, for the treatment of prediabetes. If you choose not to participate in this study, you should speak with your healthcare provider about other ways to address your prediabetes.

How will my information be kept confidential?

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. Representatives from the National Institutes of Health and the University of New Mexico Health Sciences Center Human Research Review Committee that oversee human subject research will be permitted access to your study records. Also, your participation in the study and information in your study records may be disclosed as otherwise provided by law. Information about you and your participation in this research will be maintained on a secure computer for up to 10 years after the study results have been published. However, your name will not be used in any published reports about this study.

HIPAA Information

For the purposes of determining your eligibility for this study, your electronic medical record may be reviewed. By signing this form, you are granting permission for study personnel to access your electronic medical records for the purposes of this study.

What are the costs of taking part in this study?

You will not be charged for any study procedures or treatments related to this study. The costs of Metformin, the physical exam, blood tests, body composition analysis, step-counter, and step-count diary, as well as the office visits required by the research, will be provided to you without cost. You or your third party payer (insurer) will be responsible for the costs of your standard medical care and birth control.

What will happen if I am injured or become sick because I took part in this study?

No commitment is made by the University of New Mexico Health Sciences Center (UNM HSC) to provide free medical care or money for injuries to participants in this study. If you are injured or become sick as a result of this study, UNM HSC will provide you with emergency treatment at your cost. It is important for you to tell your study doctor immediately if you have been injured or become

sick because of taking part in this study. If you have any questions about these issues, or believe that you have been treated carelessly in the study, please contact the Human Research Review Committee (HRRC) at the University of New Mexico Health Sciences Center, Albuquerque, New Mexico 87131, (505) 272-1129 for more information.

Will I be paid for taking part in this study?

In return for your time and effort participating in this study, you will be paid up to $120 if you complete the study. Specifically, you will receive a cash-card worth $30 for each of the four study visits. If you do not complete the study, you will be paid $30 for each visit you have completed. The method of payment will be via ClinCard, which is a gift card that you are free to use wherever regular credit cards are accepted.

To enable you to keep a diary of your daily step activity, you will also be provided with a pedometer (step-counter) which is yours to keep.

How will I know if you learn something new that may change my mind about participating?

You will be informed of any significant new findings that become available during the course of the study, such as changes in the risks or benefits resulting from participating in the research, or new alternatives to participation that might change your mind about participating.

Can I stop being in the study once I begin?

Your participation in this study is completely voluntary. You have the right to choose not to participate or to withdraw your participation at any point in this study without affecting your future health care or other services to which you are entitled.

If you choose to withdraw from the study, you will be asked to return your vials of study medication, and you will return to the prediabetes treatment plan that you were following prior to the study.

The study investigators may also choose to withdraw you from the study for any reason at any time during the study.

Whom can I call with questions or complaints about this study?

If you have any questions, concerns or complaints at any time about the research study, Dr. Mark Burge, MD, or his associates will be glad to answer them at 505-272-4658. We will be available Monday through Friday from 8 AM to 4 PM. If you need to contact someone after business hours or on weekends, please call 272-3183. If you would like to speak with someone other than the research team, you may call the UNM HSC Human Research Review Committee (HRRC) office at (505) 272-1129.

Whom can I call with questions about my rights as a research subject?

If you have questions regarding your rights as a research subject, you may call the UNM HSC HRRC at (505) 272-1129. The HRRC is a group of people from UNM and the community who provide independent oversight of safety and ethical issues related to research involving human subjects. For more information, you may also access the HRRC website at http://hsc.unm.edu/som/research/hrrc/ .

HIPAA Authorization for Use and Disclosure of Your Protected Health Information (HIPAA)

As part of this study, we will be collecting health information about you and sharing it with others. This information is "protected" because it is identifiable or "linked" to you.

Protected Health Information (PHI)

By signing this Consent Document, you are allowing the investigators and other authorized personnel to use your protected health information for the purposes of this study. This information may include: your name, age, height, weight, contact information, relevant information from your electronic medical record, and the fact that you do or do not have prediabetes.

In addition to researchers and staff at UNM HSC and other groups listed in this form, there is a chance that your health information may be shared (re-disclosed) outside of the research study and no longer be protected by federal privacy laws. Examples of this include disclosures for law enforcement, judicial proceeding, health oversight activities and public health measures.

Consent

You are making a decision about whether to participate in this study. Your signature below indicates that you read the information provided (or the information was read to you). By signing this consent form, you are not waiving any of your legal rights as a research subject.

I have had an opportunity to ask questions and all questions have been answered to my satisfaction. By signing this consent form, I agree to participate in this study. A copy of this consent form will be provided to you.

_____	_____/_____
Name of Adult Subject (type or print)	Signature of Adult Subject Date

I have explained the research to the subject and answered all of his/her questions. I believe that he/she understands the information in this consent form and freely consents to participate.

_____	_____/ _____
Name of Investigator or Research Team Member	Signature of Investigator or Research Team Member Date