Consent to Participate in a Research Study
Colorado State University

TITLE OF STUDY: Milk protein feeding after aerobic exercise in older adults with pre-diabetes taking the biguanide Metformin

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WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH?
If you are over the age of 55 and have fasting glucose values ≥100 mg/dl, hemoglobin A1c ≥5.7 to <6.4%, impaired glucose tolerance (glucose 2 hours postprandial ≥140 to <200 mg/dl), or a family history of type 2 diabetes then we are interested in you taking part in this study. Males and females are invited to participate. Sixty participants will be selected to participate in this study.

WHO IS DOING THE STUDY? Drs. Miller and Hamilton are Associate Professors in the Department of Health and Exercise Science at CSU and are interested in using exercise and nutrition to combat the risk of developing Type 2 Diabetes with increasing age. Drs. Miller and Hamilton will be assisted by Post-doctoral researcher Dr. Adam Konopka and graduate students of the laboratory.

WHAT IS THE PURPOSE OF THIS STUDY?
As people age, they are at an increased risk of developing Type 2 Diabetes. The anti-diabetic drug Metformin and exercise are the standard treatments to prevent Type 2 Diabetes although there is evidence that Metformin may inhibit some of the positive effects of exercise. We are interested in testing how protein from dairy products could help restore the beneficial effect of exercise when taking Metformin.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?
The study will take place in the Department of Health and Exercise Science at Colorado State University and will last three years. Total time demand for each subject is estimated at 15 weeks that includes a 12-week, supervised exercise program and dietary intervention.

WHAT WILL I BE ASKED TO DO?
The time commitment in full is explained below for each group followed by detailed procedures.

You will be expected to:

- Participate in an initial screening procedure that includes detailed review of the informed consent, physical activity and medical history questionnaire (approximately 45 min).
- Complete an oral glucose tolerance test (approximately 2 hrs).
- Perform an ECG during resting and exercise conditions (approximately 1 hr).
- Measure body weight and composition via a dual x-ray absorptiometry (DEXA) scan, followed by providing a muscle sample (once before and once after the intervention) for a total of two muscle samples for the entire study (approximately 1 hr).
- Consume labeled water during the last 4 weeks of the study (1 minute daily).
- Participate in a 12-week exercise intervention (approximately 45 min/day, 3 days/week).
- Consume a nutritional beverage (i.e, a smoothie) immediately after each exercise bout (<15 minutes).
- Optionally complete questionnaires to measure sociodemographic information, physical activity, self-efficacy, planning, self-regulation and outcome expectancy of exercise, and perceptions of neighborhood support for physical activity and participate in physical activity behavior counseling (<1 hour)
- After the 12-week exercise intervention, repeat the oral glucose tolerance test (2 hrs), DEXA scan, body weight measurement and an exercise ECG (approximately 1 hour) as well as complete the questionnaires and physical activity behavior counseling, if applicable.

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Before undergoing the sampling procedures, you will be asked a few questions related to your past and present state of health, current medication and past medical history. This is to exclude the presence of any condition or medication that might prolong your bleeding time, make blood sampling unsafe for you or be contraindicated with exercise or the drug Metformin. Following this examination, we will place a hollow plastic tube (a venous catheter) into a vein in your arm or hand. The tube will remain in your vein for over 2 hours. In total, we will sample a small amount of blood (~ 100 ml or 7 tablespoons per test). The first sample will be used to inform us if your liver and kidneys are healthy. In addition, the first and subsequent samples will be used to determine how your body regulates blood glucose after an overnight fast and after consuming a sugary drink. This test is called an oral glucose tolerance test and is commonly done in research and medical settings. A small blood sample will also be taken after week 6 to monitor liver and kidney enzymes after six weeks of metformin and/or exercise. On the advice of the medical monitor (study physician), you may be asked to have your blood tested several more times during the treatment period to make sure the study is still right for you.

If you meet the study criteria, you will also undergo cardiac screening in the presence of qualified personnel. This will involve the placement of 12 electrodes on your chest, which will be connected to an electrocardiogram (ECG). This will be done at rest and during a graded exercise test (stress test) performed on a stationary bicycle. A mouthpiece will also be used to collect the gas you are breathing during exercise. This test will measure your fitness levels and indicate whether you can safely perform the exercise intervention.

If anything adverse is found in any of the medical screening, you will be notified. A copy of your results will be available for you. You may wish to speak with your primary care physician to have the results explained to you. We will not share any information that may be used to identify you.

In the next visit, we will measure your body weight, height, and body composition by DEXA. Subsequently, a small (100-200mg, about the size of a pea) sample of muscle will be taken from one of your thighs. This will be done under a local anesthetic. A small (6-8mm or approximately 1/3 of an inch) cut will be made in your skin and another cut of the same size in your muscle. The muscle sample will be taken under sterile conditions and will be carried out by an experienced investigator (Dr. Benjamin Miller PhD, Dr. Matthew Hickey PhD, or Dr. Adam Konopka PhD) with medical oversight. Following this, pressure and ice will be applied, the incision will be secured by band-aids, then firmly bandaged with gauze. The biopsy procedure will not prevent you from performing any of your normal daily activities afterwards. After 12 hours you can remove the gauze, by three or four days the steri-strips will fall off, and the incision will heal normally like a cut. The resultant scar will gradually fade and be hardly noticeable. This visit will last about an hour.

You will be randomized to participate in 1 of 4 groups outlined in table 1 below. All groups will perform a 12-week exercise intervention. The exercise will be performed on a treadmill, stationary bicycle or elliptical for 45 minutes, 3 days per week. For the first 15 minutes, the desired exercise intensity will be 60% of your heart rate max and the next 30 minutes will progressively increase from 65 to 85% of heart rate max on a weekly basis. A trained member of the investigative team will supervise all exercise sessions by watching a heart rate monitor that you will wear during the exercise session. Immediately following each exercise bout, you will be asked to consume a ~300 calorie smoothie beverage that contains either 20 grams of protein plus carbohydrate (yogurt and fruit) or carbohydrate (fruit) only, although you will be blinded to which treatment you are assigned to.

In addition, you will be asked to consume capsule(s) consisting of either Metformin or placebo. During the first 4 weeks, the pill consumption is increased each week by 500 mg/day until a maximum dose of 2000 mg/day is reached, which is the standard therapeutic dose (see table 2). For participants with a body weight of ≤75kg, the maximum dose will be 1500 mg/day to decrease the risk of side effects. Increasing the dose slowly and consuming Metformin with food helps avoid gastrointestinal side effects.

Table 1. Outline of the four groups within this study.

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Group	Exercise	Nutrition	Drug
Group 1	12-wks Exercise	Carbohydrate	Placebo
Group 2	12-wks Exercise	Protein	Placebo
Group 3	12-wks Exercise	Carbohydrate	Metformin
Group 4	12-wks Exercise	Protein	Metformin

Table 2. Dosing scheme for both metformin and placebo

Week	Daily Dose (mg)	Number of Pills With Meal
Week 1	500	1 pill with dinner
Week 2	1000	1 pill with breakfast and 1 pill with dinner
Week 3	1500	1 pill with breakfast and 2 pills with dinner
Week 4-12	2000	2 pills with breakfast and 2 pills with dinner

During the last 4 weeks of this 12-week exercise and nutritional intervention you will be asked to drink a small volume of labeled water daily. During study week 9, you will consume a small cup of water (50 ml) three times a week, and during weeks 10-12 you will consume a small cup of water (50 ml) twice a day. The glass of water you will consume contains what is called an isotope of water. The water we provide you has a label that makes the water heavier, but imperceptible to you. This label is present naturally, but we add it in a higher concentration in order to follow metabolic reactions in the body. You will not notice this label, nor will it change anything in your body. We can only locate it by special analysis procedures after sample collection.

You will be asked to recall and record your food intake from the day before your first glucose tolerance test and then repeat the same food intake the day before your second glucose tolerance test.

A second graded exercise test as well as a DEXA scan will be completed to measure any change in fitness and body composition, respectively.

Two to three days after the last exercise session, you will repeat the muscle biopsy procedure in which a small piece of muscle will be obtained from one of your thighs.

Participants will be given the option to participate in an additional study component to determine the impact of physical activity behavior counseling following exercise training on levels of physical activity 12 weeks after the intervention ends as well as identifying individual, socio-cultural and environmental determinants of physical activity three months after the end of the exercise intervention.

If subjects decide to participate, after completion of the 12-week exercise intervention, participants will be randomized to 1) receive one session of physical activity behavior counseling (PABC), or 2) no counseling control (CON). The counseling session will consist of strategies based on social-cognitive theory. Session activities will include 1) discussion of the benefits of physical activity, 2) discussion of evidence based recommendations for frequency, intensity, time and type of physical activity for reducing the risk of type 2 diabetes and associated co-morbidities, 3) setting individual physical activity goals, 4) identifying and discussing barriers and facilitators for physical activity, and 5) identifying strategies to overcome barriers.

Table 3 Timeline of Questionnaires and Counseling Session

	Baseline	Post Intervention	Post Behavior Counseling Session	3 Month Follow-Up
Sociodemographics	X			
Physical Activity (IPAQ)	X	X		X
Self-Efficacy (EXSE & BARSE)	X	X	X	X
Planning, Self-Regulation, and Expectancy	X	X	X	X
Neighborhood Support (NEWS)	X			

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

- You should not participate if you have or have had any problems with bleeding, lung, kidney or liver dysfunction, heart failure, Type 1 or overt Type 2 diabetes, be on medication that prolongs bleeding time, or medications known to alter metabolism.
- You should not participate if you have had or are planning to have imaging that requires intravenous contrast dye (within 6 weeks) or are on any of the following medications since they are contraindicated with the use of Metformin: Dofetilide, Lamotrigine, Pegvisomant, Somatropin, Trimethoprim, Trospium, Gatifloxacin, Cephalexin, Cimetidine, Dalfampridine.
- You should not participate if you have cancer or are in remission for < 5 years.
- Because tobacco is known to affect the factors being investigated, you cannot participate if you use tobacco.
- If you are allergic to dairy products (lactose intolerant), lidocaine, or Metformin you should not participate because these items will be administered during this study.

Any change in medication (prescription or over the counter) during the study needs to be immediately reported to the study team to ensure your safety.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

These procedures are all low risk in a healthy population.

- There is a very small chance of an irregular heartbeat during exercise (< 1% of all subjects). Other rare risks of a stress test are heart attack (< 5 in 10,000) and death (<2 in 10,000). Wearing a mouthpiece and nose-clip during the graded exercise test can sometimes cause dryness in the mouth and mild discomfort.
- You are likely to experience temporary physical discomfort during the blood sampling procedure, the possibility of bruising or fainting, and an extremely slight risk of infection. Discomfort during the blood sampling is minor and brief (<30s) and bruising will not last more than one week.
- There is a small risk of infection at the site of the incision for the muscle biopsy, and a small risk of the biopsy incision reopening or bleeding after you leave the lab. The risk of allergic reaction to lidocaine (the anaesthetic used for the biopsy incision) is extremely low. There is also a risk of fainting or muscle cramp during the procedure, loss of feeling in the leg, damage to the skin (cutaneous) nerve and a risk of bruising around the biopsy site. You will have a small scar at the incision site. The rate and degree of healing varies considerably, but it is expected that scars will be difficult to see within 6-12 months after the procedure.
- The risks associated with the DEXA are very low. The maximum radiation dose you will receive in this study is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem). Put another way, the maximum dose from any scan we utilize with this DEXA ranges from 1.2 mrem (Whole body scan) to 12.2 mrem (for several of the regional scans, such as lumbar, femur, and forearm scans). The average annual background radiation you already receive is at least 620 mrem/year. The more radiation you receive over the course of your life, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation in this scan is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure.
- In a small number of cases, transient dizziness may result from the initial consumption of the heavy water.
- Metformin has the risk of causing several side effects, however, there are nearly 50 Million people in the US who use metformin on a daily basis to treat their diabetes and do not experience any side effects from Metformin use. You should be aware that metformin may cause lactic acidosis (a build-up of lactic acid in the body, that may be fatal). Lactic acidosis can start slowly and get worse over time and is more prevalent in those with liver or kidney disease or heart failure. Contact the study team and/or seek medical attention immediately if you have even mild symptoms of lactic acidosis, such as: muscle pain or weakness; numb or cold feeling in your arms and legs; trouble breathing; feeling dizzy, light-headed, tired, or very weak; stomach pain, nausea with vomiting; or slow or uneven heart rate. Call 911 or your doctor at once if you have any other serious side effects such as: feeling short of breath, even with mild exertion; swelling or rapid weight gain; or fever, chills, body aches, flu symptoms. Less serious side effects of metformin may include: headache or muscle pain; weakness; or mild nausea, vomiting, diarrhea, gas, stomach pain. It is important to stay

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hydrated (drink lots of water) while taking metformin. This is not a complete list of side effects and others may occur. Although very rare metformin may cause low blood sugar which could be masked if you are taking beta-blockers to control blood pressure. Call your doctor or ask the researchers for advice about side effects. In the US, Metformin is also known as Fortamet / Glucophage / Glucophage XR / Glumetza / and, Riomet.

- Here is a list of possible side effects of Metformin collated into most likely, less likely, rarely, and rare but serious.

- Most Likely (greater than 20%): These symptoms are generally temporary, occur during the start of treatment, and disappear without stopping the drug.
  - Diarrhea
  - Nausea
  - Vomiting
  - Abdominal bloating
  - Flatulence (gas)
  - Anorexia (loss of appetite)

- Less likely [Occasional] (5 to 20%):
  - Loss of taste or metallic taste (during start of therapy)
  - Minor weight loss (less than 1 kilogram or 2 pounds)
  - Reduced appetite

- Rarely (1 to 4%): These effects will disappear when Metformin is stopped.
  - Rash, redness or itchiness
  - Decrease in the level of a vitamin in the blood (called B12) that does not cause symptoms
  - Decrease in the red blood cell count
  - Liver function test abnormalities as seen by blood tests or hepatitis (inflammation of the liver)
  - Anxiety and nervousness
  - Depression

- Rare but Serious (less than 1%):
  - Lactic acidosis (a high acid level in the blood) occurs rarely (3 cases per 100,000 years of use) and can cause death. Individuals at risk of this complication include persons with diabetes who have kidney, liver or heart abnormalities. Symptoms of lactic acidosis may include tiredness, muscle aches, difficulty breathing, vomiting or severe abdominal pain.

- There are reproductive risks, as well, so women of child bearing potential should not become pregnant and men should not father a child.

- There are alcohol consumption risks: Participants should not drink excessive alcohol while taking the drug. There is a limit of less than 3 alcoholic beverages/day.

- It is not possible to identify all potential risks in research procedures, but the researcher(s) have taken reasonable safeguards to minimize any known and potential, but unknown, risks.

You may contact the investigators before and after working hours if you have medical concerns pertaining to study participation. Please first contact Adam Konopka at 507-602-2322 then if unable to reach Adam, please contact Benjamin Miller at 970-217-7906.

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY?
Although there are no guaranteed benefits from participating in this study. Current clinical practice includes lifestyle modifications with or without the use of Metformin as the first line of care for preventing the progression to overt Type 2 Diabetes.

DO I HAVE TO TAKE PART IN THE STUDY?

Your participation in this research is voluntary. If you decide to participate in the study, you may withdraw your consent and stop participating at any time without penalty or loss of benefits to which you are otherwise entitled.

WHAT WILL IT COST ME TO PARTICIPATE?
It will not cost you any money to participate in the study. Any treatment or medical costs that arise as a result of your participation in this study are your responsibility.

WHO WILL SEE THE INFORMATION THAT I GIVE?
We will keep private all research records that identify you, to the extent allowed by law.

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 identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private.

In the researchers' records you will be identified by a number. 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. For example, your name will be kept separate from your research records and these two things will be stored in different places under lock and key. Your identity/record of receiving compensation (NOT your data) may be made available to CSU officials for financial audits. We may be asked to share the research files for audit purposes with the CSU Institutional Review Board ethics committee, if necessary, and the Food and Drug Administration (FDA). In addition, for funded studies, the CSU financial management team may also request an audit of research expenditures. For financial audits, only the fact that you participated would be shared, not any research data.
A description of this clinical trial will be available on http://www.ClincialTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

CAN MY TAKING PART IN THE STUDY END EARLY?
If you are not compliant with any aspect of the intervention, including the exercise training, or if you miss too many appointments, you will be removed from the study.

WILL I RECEIVE ANY COMPENSATION FOR TAKING PART IN THIS STUDY?
You will receive free heart screening, stress test, comprehensive blood panel, oral glucose tolerance test and DEXA scan. At the completion of the study you will receive $500 for your participation. If you do not complete the study, you will be compensated $20 for each oral glucose tolerance test completed and $50 for each muscle sample obtained.

WHAT HAPPENS IF I AM INJURED BECAUSE OF THE RESEARCH?
We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care. The Colorado Governmental Immunity Act determines and may limit Colorado State University's legal responsibility if an injury happens because of this study. Claims against the University must be filed within 180 days of the injury.

WHAT IF I HAVE QUESTIONS?
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 about the study, you can contact our laboratory at 970-491-7913, Dr. Adam Konopka at 970-491-7193 or Dr. Benjamin Miller at 970-491-3291. If you have any questions about your rights as a volunteer in this research, contact the CSU IRB at: RICRO_IRB@mail.colostate.edu; 970-491-1553. We will give you a copy of this consent form.

If you are interested in participating in the additional study component please check the box below. You may still participate in this study if you do not wish to complete this additional study component.

☐ Wear a continuous glucose monitor (CGM) for 10 consecutive days at three different time points (before, during, and after intervention for a total of 30 days) to measure and record your glucose values every 5 minutes during those 10 day blocks of time.

☐ Complete questionnaires to measure sociodemographic information, physical activity, self-efficacy, planning, self-regulation and outcome expectancy of exercise, and perceptions of neighborhood support for physical activity and participate in physical activity behavior counseling.

Your signature acknowledges that you have read the information stated and willingly sign this consent form. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing 7 pages.

_____ _____
Signature of person agreeing to take part in the study Date

_____
Printed name of person agreeing to take part in the study

_____ _____
Name of person providing information to participant Date

_____
Signature of Research Staff