Exercise Dose and Metformin for Vascular Health in Adults With Metabolic Syndrome

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RUTGERS
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CONSENT TO TAKE PART IN A RESEARCH STUDY

Title of Study: Exercise dose and metformin for vascular health in adults with metabolic syndrome

Principal Investigator: Steven K. Malin, PhD

Study Summary: This consent form is part of an informed consent process for a research study and it will provide information that will help you decide whether you want to take part in this study. It is your choice to take part or not. Overall, the purpose of this study is to evaluate whether combining different intensities of exercise with metformin has the potential to outperform either exercise intensity alone and improve blood flow in individuals with metabolic syndrome. Metformin is a common drug provided to people to manage blood glucose. It is unclear how metformin interacts with exercise. People will be asked to visit Rutgers University about 58 times. Nearly 50 of these visits are for supervised exercise training. Before and after the intervention, metabolic and vascular health will be assessed primarily in the Clinical Research Center (CRC) at Robert Wood Jonson Medical School. Visits will range from approximately 1 to 6 hours to perform a 1) screening, 2) test of aerobic fitness and body composition, 3) insulin action on the body to manage glucose and blood flow as well as 4) a glucose tolerance test to see how the body handles clearing glucose from the blood. Tests performed before the intervention will be repeated afterwards. Further, we will repeat health measures following an 8 week follow up period after the 16 weeks of exercise and placebo or metformin. People will be randomized to these treatments (e.g. flipping a coin). There are no direct benefits for participating in this study and your alternative to taking part in the research study is to not participate.

The information in this consent form will provide more details about the research study and what will be asked of you if you choose to take part in it. If you have any questions now or during the study, if you choose to take part, you should feel free to ask them and should expect to be given answers you completely understand. After your questions have been answered and you wish to take part in the research study, you will be asked to sign this consent form. You are not giving up any of your legal rights by agreeing to take part in this research or by signing this consent form.

Who is conducting this study?
Dr. Steven K. Malin, PhD is the Principal Investigator of this research study. The Principal Investigator has the overall responsibility for the conduct of the research. However, there are often other individuals who are part of the research team.

Dr. Malin is located at 70 Lipman Dr, Loree Gymnasium New Brunswick NJ 08901 and may be reached at: (848) 932-7059 or steven.malin@rutgers.edu.

The Principal investigator or another member of the study team will also be asked to sign this informed consent. You will be given a copy of the signed consent form to keep.

Sponsor of the Study
National Institutes of Health (NIH) as well as School of Arts and Sciences at Rutgers University

Why is this study being done?
Nearly 40% of people in the U.S. have metabolic syndrome. Metabolic syndrome is the name for a group of risk factors that raises your risk for heart disease and other health problems, such as type 2 diabetes and strokes. These risk factors include a large waistline, high levels of fat in the blood, high blood pressure and high fasting blood sugars.

A large study funded by the National Institutes of Health showed that people with metabolic syndrome can dramatically reduce their risk for getting type 2 diabetes by increasing physical activity and/or losing weight. The same study also showed that treatment with metformin, a drug commonly used FDA approved drug to treat type 2 diabetes, was also effective in

reducing risk for developing cardiovascular disease. Although metformin is not as effective as physical activity, taking a pill is usually much easier for people to accomplish compared with maintaining a high level of physical activity.

The purpose of this study is to evaluate whether combining different intensities of exercise with metformin has the potential to outperform either exercise intensity alone and improve blood flow in individuals with metabolic syndrome. If so, it is conceivable that individuals can greatly reduce their risk for developing type 2 diabetes and/or cardiovascular disease by adding manageable amounts of physical activity and taking the drug metformin. Information that is gathered from this study could potentially lead to the development of treatments that specifically target cardiovascular risk reduction.

The use of Metformin in this study is considered investigational. It has not been proven by the Food and Drug Administration (FDA) for the purpose being used in this study. Currently, it is approved for people who are diagnosed with Type 2 diabetes. If you choose to participate in this study and are randomized to the metformin group, you will be given regular metformin, rather than metformin ER (extended release).

Who may take part in this study and who may not?
You are being asked to be in this study because you are a non-smoking adult with metabolic syndrome. Individuals 40-80 years are eligible with a body mass index of 25-47 kg/m2 who are not currently engaged in > 150 minutes a week of exercise may participate. Following blood work to confirm not having type 2 diabetes or kidney/liver disease, people will be required to have at minimum high waist circumference that may be accompanied by the following risk factors: high blood sugar, high blood pressure, high triglycerides or low HDL. If you are on medication for blood pressure or blood fats, then they count as risk factors. People having taken metformin in the last year, who are not weight stable, have history of significant disease (e.g. congestive heart failure, cancer, etc.), on weight suppression medication or known hypersensitivity to perflutren are not eligible for safety reasons.

Why have I been asked to take part in this study?
Your participation in this study is voluntary and you are not obligated to participate. We are recruiting participants through flyers and newspapers. Those who are eligible that call the inquiry phone number at (848) 932-9525 will reach the study team. At the time of the phone call, researchers will record your name, contact information, and walk you through a pre-screening questionnaire to determine if you meet the study criteria. Also, you and the researcher will determine a time for a screening visit to further discuss study eligibility and informed consent. All information is kept in a locked file cabinet in the lab office.

How long will the study take and how many subjects will take part?
Your participation in this study will require about **58** study visits over about 7-8 months. Each visit will last between **1-6** hours depending on whether it is for research purposes (e.g. about 3-6 hours) or exercise training (e.g. 1-1.5 hours). There are 2 Screening Visits and 5 Test Visits. Thus, the majority of visits include exercise training (48 visits).

Up to **100** people will be in this study.

What will I be asked to do if I take part in this study?
Note: All assessments outlined in this consent are being done for research purposes only. In light of COVID-19, we will follow routine safety checks per University guidelines until otherwise deemed unnecessary. These checks will be implemented at time of in person visits and consist of: temperature check and questions related to exposure yourself or to others with COVID-19. Face masks should also be worn unless otherwise indicated.

PHASE 1: SCREENING AND TESTING PROCEDURE
*Note: Portions of screening visits 1 and 2 can be combined to ease your burden and number of visits.

Screening Visit 1 at the Clinical Research Center (CRC) or Institute for Food, Nutrition and Health (IFNH) (1-2 hours)

If you agree to participate, you will sign this consent form before any study related procedures take place. Before you can start in the study, there will be a screening period as described below. You are to be fasted (nothing to eat or drink after midnight) for blood work. These include the following:

- Health history and Physical Activity Readiness Questionnaire (PAR-Q)
- Vital signs (blood pressure, heart rate)
- Height, weight, and waist circumference
- Blood draw
- Body mass index (BMI) calculation

PLEASE NOTE: Your continued participation in the study after this point will depend on the results of the vital signs, waist measure as well as blood sugar and lipid results. Further, if you are a woman who is able to bear a child, you will have a pregnancy test that must be negative in order to participate – this will be determined via bloodwork.

Screening Visit 2 at the Clinical Research Center (CRC) or IFNH or Foran Hall (1-2 hours)

IMPORTANT: You must fast (not eat or drink anything except water) for 4-10 hours before this visit. During the second screening visit the following assessments will take place:

- Medical history review
- Physical exam and vital signs (blood pressure, heart rate)
- Resting electrocardiogram (ECG)

If you continue to qualify for the study the remainder of the visit will involve the study procedures described below:

A. Body Composition and Resting Metabolism:

- Weight will be measured with minimal clothing and without shoes
- Waist and hip circumference ratio measured
- DEXA scan to measure amount of fat and muscle
- Note: You must wear clothes without metal on them (including zippers and bras with an underwire). If your clothes have metal, we will ask that you change into a pair of shorts and a t-shirt or wear a hospital gown provided by the lab.
- If there are technical issues with the DEXA machine, we will use the BodPod® in the IFNH. We will provide a swimsuit and swim cap for you to wear during this procedure to help provide accurate results. You will not get wet at any time during this measurement. You will enter the device, sit down, and asked to be still and breath normally. The door will close, but there is a window.
- Resting metabolic rate measurement will help determine food needs. While laying down you will wear a canopy that is connected to a metabolic cart.

B. Treadmill exercise testing for cardiovascular fitness (i.e. VO2max):

- The test will begin with low speed on the treadmill, and the resistance will increase gradually every 2 minutes. You will be asked to go as long as you can, that is, until you feel exhausted.
- During the test, you may have continuous electrocardiogram (ECG) heart monitoring and blood pressure monitoring
- You will wear a facemask over your nose and mouth to measure how much oxygen you are using and fitness level. You will also be provided with an **accelerometer** (to record activity) and instructions on how to use it.

C. Questionnaires

- Physical activity and enjoyment
- Quality of life
- Sleep history
- Mental health
- Appetite
- Diet logs (daily record for 3 days at the weeks below)
- Emotional eating

All questionnaires will be completed during weeks 0, 4, 8, 12, and 16. A Morningness-Eveningness questionnaire will be completed at weeks 0 and 26 along with the Veteran Rand-36 about overall happiness (also week 8). The Three-Factor Eating questionnaire will be completed at weeks 0, 8, 16, and 24.

PHASE 2: TESTING CONDITIONS AND PROCEDURES

Study test Visits 3 and 4

- You will be asked to maintain your normal activity levels
- You will be provided standardized meals and snacks the day prior to and during all blood test visits
- You will be asked to report to the CRC by approximately 6:30-9:00am on the morning of each test
- You must **not**:
    - Drink alcoholic or caffeinated beverages for at least 24 hours before the study testing visit begins
    - Use allergy, prescription or pain-related medicines (over the counter or prescription) or antioxidant dietary supplements for at least 24 hours prior to each testing visit. Prescription meds may be taken after testing.
    - Perform any vigorous exercise (outside of this training study) for 72 hours prior to each test day.
    - Take antibiotics 3-4 weeks before study testing. If you have been prescribed an antibiotic before or during the study, please inform the research team.
    - Eat or drink anything (except water) after about 9:00pm the night before.

Pre and Post Study Testing days:

Blood draws:

- An IV (intravenous) catheter will be inserted to measure sugars, lipids, and hormones
- You will be fed lunch before you go home
- The amount of blood collected pre and post study is approximately a pint.the same as donating a pint of blood. You are advised not to donate blood while participating in this study.
- Visit 3 and visit 4 tests will be performed about 24 hours or more apart.

Glucose Metabolism test (i.e. blood sugar): Visit 3 or 4, 54 or 55, and 58

Oral Glucose Tolerance Test (OGTT) (approximately 4 hours)

- The OGTT is used to help determine how quickly sugar is removed from the blood
- You will report to the CRC fasted (about 10 hours) and we will put an IV in for baseline blood samples
- You will drink a sugary solution
- Five more blood draws will be taken at 30, 60, 90, 120, and 180 minutes.
- At 0, 60, and 120 minutes we will measure blood flow using the methods below
- You will complete items on the NIH toolbox for related to working/episodic memory, executive function and attention. The NIH toolbox is an iPad application that consists of cognitive, emotional, motor and sensory function assessments. This will take about 20 minutes and will be completed prior to consuming the sugary solution and after the 120-minute mark.

Euglycemic-Hyperinsulinemic Clamp "Clamp" (approximately 6 hours – separate visit)

- This test is the gold standard for measuring insulin sensitivity
- You will report to the CRC fasted (about 10 hours) and you will have two IVs in your arm
- Medications/vitamins can be taken after the test and you will be given a meal at the end
- We will inject a non-radioactive glucose tracer 2 hours before and after the clamp to determine how insulin is acting on various tissues. The tracer contains a small amount of heavy hydrogen, which is naturally present in your body.
- Insulin will be infused at a constant rate and a variable amount of glucose will be infused to keep you at a normal blood sugar level. Blood will be drawn every 5 minutes to ensure this.
- You will also have a see-through canopy (cover) over your head before and at the end of the clamp. This procedure uses the same machine used during exercise in screening visit 2, part B above.

Urine Collection:

- You will be provided with a plastic container and asked for a urine sample on visits 3 and 4. We will look at nitrogen, protein and metabolite concentrations.

Blood flow to be done at Visit 3 and/or 4, 54 and 58:

Blood pressure:

- Your blood pressure will be taken at the beginning of each visit.

Large artery flow-mediated dilation (FMD):

- An ultrasound will be used to measure blood flow in the brachial (arm) and femoral (leg) artery.
- Just prior to the test you will be asked to lie down on a bed quietly for 20 minutes. During this time, you will have your blood pressure taken, and you will be connected to an electrocardiogram (ECG). After the 20 minutes have passed, the ultrasound will take images of the arteries.
- Next we will place a blood pressure cuff on your forearm only and pump it up tightly. This portion of the test may cause some discomfort in your forearm and fingers (such as pain, tingling, and numbness).
- We will keep the cuff inflated for 5 minutes, take images, then release it, and measure the increase in blood flow.
- We will perform this procedure just before the glucose beverage during the OGTT, and then again at 1 and 2 hours afterwards. For the clamp test, we will perform this once at the beginning and end

Heart Images:

- Prior to the test you will be asked to lie down on a bed quietly for 20 minutes. We will measure vitals, ECG, and heart rate. After 20 minutes, we will use the ultrasound to measure heart size and function.
- We will perform this procedure just before the clamp or OGTT method. If neither time is possible, a separate visit may be necessary.

Augmentation Index (AI):

- This measures stiffness in the aorta. It is done by placing a blood pressure cuff on your upper arm. It is inflated three different times.

Pulse Wave Velocity (PWV):

- This measures the stiffness in larger vessels. A blood pressure cuff will be placed on your upper thigh and a doppler pen placed on the carotid artery in the neck. This will assess travel time of blood from neck to the thigh.

Contrast Enhanced Ultrasound (CEU):

- This is used to look at muscle and heart blood flow at the microcirculation (or closest part of blood flow to muscle/heart).
- We will infuse the microbubbles that are approved by the FDA for imaging of the microvasculature.

The AI, PWV, and CEU measurements are done at the pre-intervention (0 weeks), post-intervention (16 weeks), and at the 8-week follow-up (24 weeks). They take place during the start and end of the OGTT and clamp visits.

RANDOMIZATION and STUDY PROCEDURES

Prior to the intervention you will be randomized (like the flip of a coin) to receive 1 of 4 treatment options for 16 weeks. Neither you nor your doctor can choose which treatment you are assigned and both will find out when the study is done. If your doctor needs to know whether metformin or placebo pill is prescribed due to medical reasons that directly affect your medical treatment, the people doing this study can find out. The groups are described below.

PHASE 3: INTEREVENTION PERIOD (Visits 5-53)

Ambulatory Blood Pressure (before intervention and in the last week):

- This is used to look at blood pressure throughout the entire day and night for 24 hours.
- This measure occurs using a blood pressure cuff that is wrapped around your arm with a holter monitor secured to your belt.
- You are instructed to go about your normal activities throughout the day.
- During periods of inflation and deflation, we ask you to relax your arm.
- This will occur before the first training session.
- At the same time you will be given meals to follow for the 24-hr collection period.

Note: Due to COVID-19 if supervised exercise sessions need to vary for safety reasons, virtual sessions will be established within reason to maintain "supervised" sessions.

- Low Intensity Exercise Training (LoEx) + Placebo
- High Intensity Exercise Training (HiEx) + Placebo
- LoEx + Metformin
- HiEx + Metformin

LoEx + Placebo: You will be asked to attend 3 regularly supervised and scheduled training sessions (e.g. M, W, and F) with the exercise physiology staff at the Loree Gymnasium or IFNH on Cook-Douglas Campus. On the remaining 2 days a week (e.g. T and Thr) you will be instructed to exercise on your own for half the time that you do in the supervised training sessions. Your heart rate will be monitored continuously, and you will be asked to exercise at an intensity near 50-55% of your previously measured fitness level. The amount of time you exercise will vary based on capacity to burn 400 kcal on supervised days and 200 kcal on unsupervised days. During the first days of training we will measure breath samples during exercise to ensure proper exercise intensity and determine how many calories from sugar and fat you are burning for energy. Every 4 weeks you will have your body weight and waist circumference measured prior to a training session. In addition to this training program you will be provided a placebo. The placebo is a harmless substance that looks like the study drug, but which should have no effect. Pills will be provided to you by the research team as prepared by Rutgers Pharmacy in the CRC on a weekly basis. Unused pills should be returned to our research team. At weeks 0, 8 and 16, accelerometers will be provided.

HiEx + Placebo: You will participate in exercise training just as described above. However, the exercise training intensity based on your heart rate will be near 85%. Exercise duration will vary in order to expend the same number of calories described above. You will be provided a placebo and accelerometer.

LoEx + Metformin: You will participate in the same LoEx exercise program as outlined above. But, you will be provided metformin.

HiEx + Metformin: You will participate in the same HiEx exercise program and receive metformin.

PHASE 4: POST INTERVENTION TESTING (Visits 54-56)
After the 16 week intervention you will be asked to undergo the same series of testing that you completed in phase 2. You will be asked to take the same precautions before to testing as described above. All study testing visits highlighted above in Visits 2, 3 and 4 will be repeated (except physical screening and resting EKG). The order of the tests post-intervention will be:

1. Clamp Study (Visit 54)
2. OGTT (Visit 55)
3. Body Composition and Fitness (Visit 56)

Visits 53, 54 and 55 will be on consecutive days.

*Intervention (medication and exercise) may be extended or shortened by approximately one week if scheduling requires to complete visits 54 and 55 of post-intervention testing at a different time.

PHASE 5: Unsupervised Exercise Follow-up (Visit 57-58)
After the post-intervention testing, you will be asked to exercise on your own (e.g. purchase a gym membership, etc.) while wearing the polar activity tracker watch and heart rate strap. We ask that you exercise at the same intensity that you have been exercising with us during the intervention. We will check in by phone within week 2 to see if you are exercising, or if there are any complications.

Visit 57
During week 4, you will come to Loree Gymnasium/IFNH to check in with the study team. At this visit you will receive an accelerometer to wear for 7 days, 3-day diet logs to fill out, and will have waist circumference and weight measured. We will provide you a pre-stamped envelope to return the diet log and accelerometer within 7 days.

Visit 58 (about week 8-10) approximately 6 hours
You will return the above mentioned items at your testing visit as well as your heart rate strap.

A. OGTT

- See page 4

B. Treadmill Exercise Testing (VO2max)

- See page 3

C. Body Composition and Resting Metabolism

- See page 3

NOTE: In the event of scheduling conflicts, cardiovascular fitness and/or body composition assessments may be completed within about 1 week of doing the OGTT during Visit 58.

END OF STUDY:

After subjects have completed Phase 5, the study will be complete.

What are the risks of harm or discomforts I might experience if I take part in this study?

Research studies often involve some risks. We will do all we can to prevent bad results for you.

Risks and side effects related to the study procedures include:

Likely

- Fatigue and soreness from exercise
- Soreness from IV catheter placement
- Mild to moderate discomfort (e.g. pain, tingling, and/or numbness) in the forearm and hand from the inflated blood pressure cuff (approximately 5 minutes)

Less Likely

- Mild skin irritation from electrode application for the heart monitor
- Possible unpleasant reaction to the glucose drink (ex. nausea or feeling sick to your stomach)
- Potential overuse injury from exercise (pain in leg muscle/tendons)

Rare but serious risks related to exercise

- Abnormal blood pressure responses
- Faintness, dizziness, disorders of the heartbeat
- Heart attack, stroke, or even death (the risk of death during or immediately after an exercise test is less than 1 in 10,000). Every effort will be made to minimize risks by observations during each exercise session. Emergency equipment and trained exercise physiologists will be present during the exercise tests.

Blood draw and Intravenous catheter placement (IV): Need insertion may cause some common temporary pain or bruising and some people may feel dizzy. To prevent infection, your skin is cleansed prior to needle insertion and only sterile needs are used.

If the people doing the study are exposed to your blood or body fluids in a way that could give them a disease, your blood may be tested for hepatitis, HIV (Human Immunodeficiency Virus), or other infections. You and the person exposed would be told the test results and your name would be kept private. If your test is positive for hepatitis or HIV, we will tell you how to find counseling and resources.

ECG: Men may need to have a small amount of chest hair shaved off for the ECG pads to stick correctly. A small amount of adhesive might remain on your skin when the pads are removed, or the adhesive might pull on hair when removed. You can easily remove any remaining adhesive with rubbing alcohol or soap and water.

Urine Collection: There are no risks to collecting urine samples.

Risk of Saline Flush: Saline is a salt solution that helps to prevent blood clots from forming in the IV catheters. There may be some mild pain at the injection site.

Study Diet: You might have to fight cravings to eat or drink items that are not part of the approved and provided research diet.

Questionnaires: There is the potential risk of loss of confidentiality. Every effort will be made to keep your information confidential, however, this cannot be guaranteed. Some of the questions we will ask you for this study may make you feel uncomfortable.

Accelerometer: You might find it uncomfortable to wear the activity monitor for extended periods of time.

Indirect Calorimetry: For some people, the plastic canopy over their heads/mouthpiece makes them feel claustrophobic or anxious. This feeling is temporary and will go away when the canopy is removed. The canopy is "see through" and does not restrict movement.

Oral Glucose Tolerance Test: You could react to the ingestion of nutrients, namely glucose. These reactions could include nausea, low blood sugar, and an increase in blood pressure, flushing and/or sweating.

Definity Microbubbles: Occasionally you could experience flushing and temporary altered taste sensation. Back pain occurs in 1-3% of subjects, although this resolves within 1-5 min after stopping the microbubble infusion. The infusion will be stopped in anyone noting onset of back pain during the microbubble infusion. Heart and lung blood shunting of microbubbles is a potential concern, however it is very unlikely. To avoid the slight possibility of an anaphylactic reaction (fever, drop in blood pressure, shortness of breath), solutions are sterile prior to infusion.

Serious cardiopulmonary and hypersensitivity reactions are rare, but may occur, including fatal heart or respiratory attack, shock, loss of conscious, arrhythmias, hypertension (high blood pressure), convulsions, throat tightness, swelling of the face, eye, upper airway, rash and flushing.

In the event of a medical emergency, study personnel will call the Rutgers Emergency Services line and call the physician on call for immediate assistance.

Clamp Test: Glucose and insulin administration during the euglycemic-hyperinsulinemic clamp procedure can cause transient hyperglycemia or hypoglycemia. There is a slight possibility that infusion of insulin will lead to hypoglycemia (low blood sugar). Subjects may experience a headache, dizziness, feel faint, hunger, confusion or, if these early symptoms are not treated, could lose consciousness. To minimize the risks, blood sugar levels will be monitored every 5 minutes to make sure that subjects do not become hypoglycemic. As an added precaution, a physician/nurse will be in the room or close at hand (in the building) during these tests.

Isotope Tracer Infusion: Infusion of stable isotope tracers includes a slight possibility of an anaphylactic reaction (fever, drop in blood pressure, shortness of breath) if the solutions contain impurities. To minimize this risk, all solutions are prepared under sterile conditions. The isotopes used in this study as tracers are present in your body naturally. They have been approved for research purposes by the US Food and Drug Administration (FDA).

Metformin: To minimize the possibility of side-effects, the dose of your medication will be gradually increased, under the medical supervision of Dr. Shah and Wondisford, every week until you are taking 2 pills per day (total dose of 2000 mg metformin). In very rare cases, metformin can cause a serious side-effect called lactic acidosis. Signs of lactic acidosis include feeling very weak or tired, unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, dizziness or lightheadedness, or suddenly developing a slow or irregular heartbeat. If you experience any of these symptoms or if you have any questions about them, please call the study coordinator immediately (848-932-9525) or Dr. Shah (732 401-5445). Lactic acidosis is a very serious medical condition that may be fatal. You should not take metformin if you are pregnant or have any kidney problems, liver impairment, or are on certain drugs (e.g. Glyburide, Furosemide, Nifedipine, and Catonic drugs). Your health history will be reviewed by Dr. Shah or Wondisford and they will be monitoring your well-being while you are taking the drug. You should avoid alcohol while on metformin.

More common mild side effects of metformin include diarrhea, nausea, upset stomach, and abdominal pain. Hypoglycemia (low blood sugar) is possible but unlikely unless you do a lot of vigorous exercise or severely restrict the amount of carbohydrates in your diet. We will counsel you regarding appropriate exercise and nutrition habits during this study. Symptoms of mild to moderate hypoglycemia include fatigue, lightheadedness, mood changes, hunger, clammy hands

and/or feet. Some of these side-effects are similar to normal everyday experiences (for example hunger or fatigue). If you experience any of these symptoms and they seem unusual or if you have any question about them, please call Dr. Shah immediately (732-235-7219). It is better to be overly cautious so do not hesitate to call if you are unsure. Severe hypoglycemia is extremely unlikely but if it occurs, it is a serious medical condition that can lead to unconsciousness. About 3 out of 100 people have an unpleasant metallic taste when they start taking the medication, but it usually lasts for only a short time.

DEXA Scan: This study involves radiation exposure from DEXA scans of your whole body. The radiation dose you will receive from this study is considered small.

Reproductive Risk: If you become pregnant during the course of this study, you should notify the study doctor of this fact as soon as possible. While there no evidence of birth defect or complications, you will be encouraged to exit the study.

Drug to drug interaction: You should share prescribed medicines, over-the-counter medicines, herbal products, vitamins or food supplements prior to starting this study and avoid new drugs unless you tell the study doctor and get permission from the study doctor to go on taking these medicines. You will follow the instructions of the study doctor about the use of any of these products.

A caution about giving too much blood:
Because of the amount of blood being taken, you should not give blood for other reasons while in the study. You should wait 2 months after the study is completed before donating blood at a blood bank.

Unforeseeable risks: There may be risks or side effects related to the study that are unknown at this time. You will be notified of any significant new findings that become known that may affect your willingness to continue in the study. Contact the study project manager (Jaclyn Dosik, 848-932-7059; jaclyn.dosik@rutgers.edu) if you have any symptoms or problems.

Are there any benefits to me if I choose to take part in this study?
You may or may not benefit from being in this study. However, some possible benefits to you include: knowledge of fitness, body fat, metabolism, blood sugars and cardiovascular health. In addition, information researchers get from this study may help others in the future. Society in general will benefit from greater understanding of the importance of exercise at low or high intensity with metformin for improving vascular function, insulin-stimulated glucose uptake as well as hypertension and circulating glucose control.

What are my alternatives if I do not want to take part in this study?
You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment even if you choose not to be in this study. The usual treatment would include careful follow-up with your primary care physician.

How will I know if new information is learned that may affect whether I am willing to stay in the study?
During the study, you will be updated about any new information that may affect whether you are willing to continue taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will I receive the results of the research?
During the study your study leader will let you know of any test results that may be important to your health. In addition, as the research moves forward, your study leader will keep you informed of any new findings that may be important for your health or may help you decide if you want to continue in the study. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time you can ask for more information about the study results. For instance, upon completion you will receive a report detailing your individual results (e.g. body composition, fitness, effects of exercise on post prandial hyperglycemia).

Will there be any cost to me to take part in this study?
All of the tests outlined this research study will be provided at no cost to you or your health insurance. You will be responsible for the cost of travel to come to an y study visit. You will be provided parking costs.

Will I be paid to take part in this study?
You will be compensated up to $1650 for completion of the study, made either in 4 payments scheduled throughout your study visits or a total sum at the end of the study. You will receive payments based on your selection below. You will be paid by check distributed by the study team. The income may be reported to the IRS as income. Appropriate tax documentation will be provided.

Completion of Phase 3:	$200
Completion of Phase 3(with isotope):	$300
Completion of Phase 4:	$600
Completion of Phase 4 (with isotope):	$700
Completion of Visit 57:	$200
Completion of Visit 58:	$300
Total payment:	**$1,300 (without isotope) or $1500 (with isotope)**

*Will be able to keep Polar HR monitor at the end of the study. (~$150)

_____ Please check here if you would like to receive compensation, based on the outline above, at the completion of each phase.

_____ Please check here if you would like to receive compensation, based on the outline above, at the completion of your time in the study.

By agreeing to be in this study, you are donating your blood for research, and giving up any property rights you may have in them. The results of this research using your donated materials may have commercial value. However, you will not receive any payments.

How will information about me be kept private or confidential?
All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed. This includes keeping files in locked cabinets, rooms and using password protected devices. Moreover, you will be provided an ID number that minimizes use of your name to protect privacy/confidentiality.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

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 Web site will include a summary of the results. You can search this Web site at any time.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require, such as laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

What will happen to my information or biospecimens collected for this research after the study is over?
After information that could identify you has been removed, de-identified information collected for this research may be used by or distributed to investigators for other research without obtaining additional informed consent from you.

What are your responsibilities in the study?
You have certain responsibilities to help ensure your safety, including:

- You must be completely truthful about your health history.
- Follow all instructions given.
- You should tell the study doctor or study staff about any changes in your health or the way you feel.
- Answer all of the study-related questions completely.
- Inform the study doctor or study staff as soon as possible if you have to take any new medications, including anything prescribed by a doctor or those that you can buy without a prescription (over-the-counter), including herbal supplements and vitamins. The study doctor will let you know if you can take these medications.
- You cannot drink alcohol 24 hours prior to study tests and are advised to avoid alcohol throughout the entire study.
- You cannot eat or drink foods that contain caffeine 24 hours prior to study tests. Common foods containing caffeine include coffee, tea, soda and chocolate. If you have questions on foods containing caffeine, please ask one of the team members before your study begins.
- We also ask that you refrain from any structured exercise for 24 hours prior to testing and limit exercise to your normal everyday activities.

What will happen to my information or biospecimens collected for this research after the study is over?
Research samples will be collected on the day of your research visits. We will take 1½ tablespoons of blood during Visit 1, about 7 tablespoons during the oral glucose tolerance test, and about 16 tablespoons during the clamp study. After the tests for the study are completed, there may be samples left over. Normally, these leftover samples would be thrown away. We are asking you to allow us to collect this leftover material for specimen banking.

You are being asked to provide samples of your blood to be used for future research. Along with specimens, researchers may need to collect some health information about you. Combining information from the specimen with information from your health records may be useful for this research. For this research, the following types of information could be included: vital signs, lab results, age, gender, medications you are taking, whether or not you have diabetes, family history of cardiovascular disease and other known medical disease.

In addition, if you agree, specimens collected for research will be added to a research specimen bank. The purpose of a specimen bank is to process, and store samples until researchers need them for future research. The long-term goals of the samples collected in this bank will be mainly used for research on diabetes and cardiovascular disease prevention. It is not possible, however, to list every research project that will include the samples because we cannot predict all of the research questions that will be important over the coming years. As we learn more, new research questions and new types of research may be done.

What will happen if I am injured during this study?
In this study, you will be exposed to certain risks of personal injury in addition to those associated with standard forms of treatment, which include descriptions outline above in “risks”. In addition, it is possible that during the course of this study, new adverse effects of exercise/metformin/placebo may occur that result in personal injury may be discovered. The University will make appropriate referrals for medical and/or dental treatment for subjects who sustain personal injuries or illnesses as a direct consequence of participation in the research. The subject’s health insurance carrier or other third-party payer will be billed for the cost of this treatment; provided that the University shall not submit to federally funded programs, e.g., Medicare, Medicaid or CHAMPUS, for reimbursement first if submission to such programs is prohibited by law. No financial compensation will be provided by the University and no other type of assistance is available from the University. However, by signing this form, you are not giving up any legal rights to seek further compensation.

What will happen if I do not wish to take part in the study or if I later decide not to stay in the study?
It is your choice whether to take part in the research. You may choose to take part, not to take part or you may change your mind and withdraw from the study at any time.

If you do not want to enter the study or decide to stop taking part, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include

a) Your study physician is concerned about your health
b) You do not follow the instructions of the study doctor or study staff
c) The study sponsor closes the study for safety, administrative or other reasons

If you decide to stop being in the study, we will ask you to contact the study coordinator (contact information listed below) by telephone, email, or written letter.

If you decide to withdraw from the study for any reason, you may be asked to return for at least one additional visit for safety reasons.

Who can I contact if I have questions?
If you have questions about taking part in this study or if you feel you may have suffered a research related injury, you can contact the researchers listed below to:

Steven K. Malin, Ph.D. (Principal Investigator)
Department of Kinesiology and Health
Division of Endocrinology, Metabolism, and Nutrition
Rutgers University, New Brunswick, NJ 08901,
(848) 932-7059; steven.malin@rutgers.edu

Jaclyn Dosik, M.Ed. (Clinical Research Coordinator)
Department of Kinesiology and Health
Rutgers University, New Brunswick, NJ 08901,
(848) 932-7059; jaclyn.dosik@rutgers.edu

Mary Remchak, M.Ed. (Study Manager)
Department of Kinesiology and Health
Rutgers University, New Brunswick, NJ 08901,
(848) 932-7059; mary.remchak@rutgers.edu

Tristan Ragland, PhD, FNS (Study Manager)
Department of Kinesiology and Health
Rutgers University, New Brunswick, NJ 08901,
(848) 932-7059; tr498@kines.rutgers.edu

Daniel Battillo, B.S. (Study Manager)
Department of Kinesiology and Health
Rutgers University, New Brunswick, NJ 08901,
(848)-932-7059; daniel.battillo@rutgers.edu

Afsheen Syeda, M.S. (Study Manager)
Department of Nutritional Sciences
Rutgers University, New Brunswick, NJ 08901,
(848)-932-7059; uss10@dls.rutgers.edu

Habiba Faiz, B.S. (Study Manager)
Department of Nutritional Sciences
Rutgers University, New Brunswick, NJ 08901,
(848)-932-7059; hf218@scarletmail.rutgers.edu

EMERGENCY HEALTH CONTACT *if problems occur:*

- In case of emergency, call 911 or go to the nearest Emergency Department.
- During normal business hours, contact Dr. Shah, MD at (732) 235-6337.
- After hours or on the weekend, call (732) 401-5445 to reach Dr. Shah. Please DO NOT text as they will not be forwarded to Dr. Shah. Only phone calls please.

If you have questions about your rights as a research subject, you can contact the Rutgers IRB Director at:

Health Sciences IRB New Brunswick/ Piscataway
Office of Research Regulatory Affairs, Rutgers University
Liberty Plaza/ 3rd Floor / Suite 3100
New Brunswick, NJ 08901
732-235-9806

You may also contact the Rutgers Human Subjects Protection Program at (973) 972-1149, email us at humansubjects@ored.rutgers.edu, or write us at 65 Bergen St., Suite 507, Newark, NJ 07107.

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

PERMISSION (AUTHORIZATION) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

The next few paragraphs tell you about how investigators want to use and share identifiable health information from your medical record in this research. Your information will only be used as described here or as allowed or required by law. If you sign this consent form, you agree to let the investigators use your identifiable health information in the research and share it with others as described below. Ask questions if there is something you do not understand.

What Is the Purpose of The Research and How Will My Information Be Used?
You are being invited to take part in this research study which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help investigators answer the questions that are being asked in the research.

What Information About Me Will Be Used?

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address and date of birth.
- Your health information is required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers. This may include mental health care records, substance abuse records, and/or HIV/AIDS records.
- Social Security number ONLY IF you are being paid to be in this study

Who May Use, Share or Receive My Information?
The research team may use or share your information collected or created for this study with the following people and institutions:

- Rutgers University Investigators Involved in The Study
- The Rutgers University Institutional Review Board and Compliance Boards
- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services
- Hospital Personnel as Necessary for Clinical (e.g. Robert Wood Johnson University Hospital, Barnabas health, University hospital, etc.).

- Non-Rutgers Investigators on the Study Team (e.g. Uta Erderbrugger, Eugene Barrett, Zhenqi Liu at University of Virginia, etc.).
- The Food and Drug Administration.

Those persons or organizations that receive your information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

Will I Be Able to Review My Research Record While The Research Is Ongoing?
No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I Have to Give My Permission?
No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

If I Say Yes Now, Can I Change My Mind and Take Away My Permission Later?
Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your information in the research, you must write to the researcher and tell him or her of your decision: Dr. Steven K. Malin, PhD in the Department of Kinesiology and Health and Division of Endocrinology, Metabolism, and Nutrition at Rutgers University ((848) 932-9525; steven.malin@rutgers.edu).

How Long Will My Permission Last?
There is no set date when your permission will end. Your health information may be studied for many years.

Please see the addendum: **Consent to Store.**

AGREEMENT TO PARTICIPATE

Subject Consent:

I have read this entire consent form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form and this study have been answered. I agree to take part in this study.

Subject Name (Print):_____

Subject Signature:_____ Date:_____

Signature of Investigator/Individual Obtaining Consent:

To the best of my ability, I have explained and discussed all the important details about the study including all of the information contained in this consent form.

Investigator/Person Obtaining Consent (Print):_____

Signature:_____ Date: _____