Metformin in Kidney Disease

NCT02252081

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Dysmetabolism of Chronic Kidney Disease and Vascular Health—Aim 2

Rationale and Specific Aims for Aim 2

The ultimate goal of this proposal was to understand the relative and combined impact of obesity and CKD on the generation and maintenance of insulin resistance and their impact on cardiovascular health.

Specific Aim 2: To study the effects of metformin, an AMPK activator, on metabolic disturbances associated with obesity and moderate CKD.

S.A.2.a: To test if metformin will improve LAR in obese patients with moderate CKD compared to placebo.

S.A.2.b: To test if metformin will improve markers of systemic inflammation, oxidative stress, endothelial dysfunction (flow mediated vasodilation [FMD] by brachial doppler) in obese patients with moderate CKD compared to placebo.

S.A.2.c: To test if metformin will improve atherosclerosis markers (pulse wave velocity and CIMT) and reduce clinical CVD events in obese patients with moderate CKD compared to placebo.

Hypothesis: We hypothesize that the administration of metformin in obese CKD patients will significantly improve the adipokine profiles—particularly through a reduction in LAR. Additionally, that it will improve systemic inflammation, oxidative stress, and endothelial function (flow mediated vasodilation), which may or may not be mediated by changes in adipokines. Finally, we hypothesize that improvements in these markers of vascular health will translate into reduced arterial stiffness and less clinical CV events.

Inclusion/Exclusion Criteria

There will be no restriction on gender (except pregnant women), race, and age (except less than 18 years old) or disease etiology for patient selection or exclusion except as stated below.

Inclusion Criteria:

1. Age ≥ 18 years old;
2. Ability to give informed consent;
3. Life expectancy greater than 6 months;
4. Estimated GFR 30-59 ml/min/1.73m^2;
5. Overweight (BMI ≥ 25 to < 30 kg/m^2) or obese (BMI ≥ 30 kg/m^2); or normal (BMI ≥ 18.5 to < 25 kg/m^2) if pre-diabetic or insulin resistant.

Exclusion Criteria (all subject groups):

1. Pregnancy or breast feeding;
2. Presence or history of Diabetes Mellitus type I or II
3. History of metformin use or any insulin sensitizer or any drug for the treatment of metabolic syndrome over the last one year;
4. Any acute kidney injury episode in the last 4 months due to the risk of recurrent AKI;
5. Proteinuria of > 5 g in 24 hours determined by a 24 hour urine collection or PCR > 4.5;
6. Uncontrolled hypertension with systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥ 100 mmHg;
7. Patients with new changes to their antihypertensive regimen over the last 1 month;
8. Severe, unstable, or active inflammatory disease; active infection including seropositive HIV, Hepatitis B or C; active connective tissue disorder; or moderate to severe liver disease;
9. Decompensated heart failure;

10. Recent hospitalization or surgical procedure within 1 month prior to the study for any cause;
11. Current active malignancy or cancer history in the prior 2 years (excluding squamous cell and basal cell skin cancers);
12. Known intolerance to the study drug;
13. Patient receiving oral or injected steroids;
14. Use of any investigational product or device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments.

Enrollment/Randomization

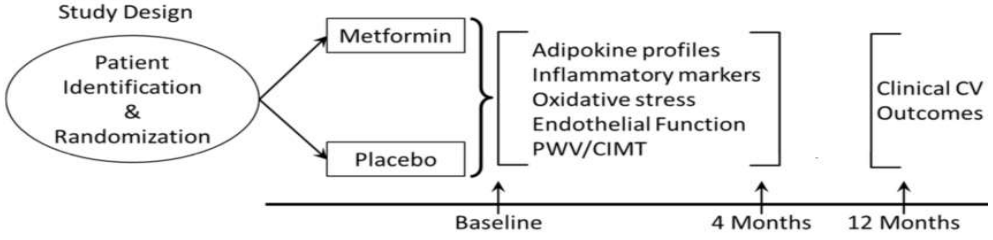
All studies will be conducted at the Vanderbilt University Medical Center General Clinical Research Center (GCRC) or at the Nashville VA Tennessee Valley HealthCare System (TVHS). Institutional review board approval have been obtained at both institutions and written informed consent from all study subjects were obtained.

Human Subjects Involvement and Characteristics: We propose to study 120 overweight or obese patients with CKD Stages 3 – 4 for Specific Aim 2. All participants will have a baseline assessment, as well as on-going monitoring, of their health status as documented in their medical record.

Study Procedures

The design is a randomized, double-blind, placebo-controlled study. Once the subject is determined to be eligible, we will randomly assign him/her to metformin versus placebo as depicted in **Figure 11**. The investigators and the study subjects will be blinded to the treatment. Each subject will be treated for 4 months (16 weeks). All of the visits will happen either at the General Clinical Research Center (GCRC) at Vanderbilt University or at the Nashville VA.

Figure 11
Study Design



Once the baseline studies are completed (see below), we will start the subjects on the randomly assigned protocol of metformin versus matching placebo. The metformin dose will be 1500 mg daily for people with eGFR > 45 ml/min per 1.73 m^2 and 500 to 1000 mg daily dose for those with an eGFR 30 to ≤ 45 ml/min per 1.73 m^2. All medications and matching placebo will be prepared and dispensed by either Vanderbilt's Investigational Drug Services (IDS) or the VA pharmacy by the investigational drug/pharmacy research team.

Table. Schedule of Procedures

Procedure	Weeks -2 to 0	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 56 Optional
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical exam	✓				✓		✓	✓	✓
Blood collection	✓	✓	✓	✓	✓	✓	✓		
Urine collection	✓	✓		✓	✓		✓		
Urine protein	✓								
Urine creatinine	✓								
OGTT		✓							
CMP (fasting)	✓			✓	✓	✓	✓		
Glycohemoglobin	✓								
Lipid panel	✓						✓		
CBC	✓				✓		✓		
Lactic acid		✓	✓	✓	✓	✓	✓		
Serum Pregnancy test		✓							
DEXA		✓							
Brachial artery Doppler (FMD)		✓					✓		
PWV		✓					✓		
CIMT		✓					✓		
Questionnaires		✓					✓		
LDF (optional)		✓					✓		
Study drug/placebo dispensing		✓		✓	✓	✓			

Screening Visit: Within about two weeks up to the start of the Treatment Phase (which begins at the Baseline Visit) and after the subject has provided informed consent, the subject will be asked to come in fasting state and the following information will be collected:

- Inclusion/exclusion
- Demographics
- Medical history
- Concomitant medications

Also, the following procedures and assessments will be performed:

- Vital signs
- Physical exam (may be performed instead at Baseline Visit)
- If a subject has had a CBC (complete blood count) test within 2 weeks of the stipulated study entry date as part of routine medical care, this value will be counted as the screening value and entry value will be drawn at the Baseline Visit.
- If CBC is drawn for screening, it will be counted as entry value at the Baseline Visit.

- CMP (comprehensive metabolic panel fasting state), liver function test, glycated hemoglobin, and lipid panel
- Urine protein and creatinine

Baseline Visit (Week 0): Subjects that qualify for the study will be asked to come in a fasted state. At the Baseline Visit, the following information will be collected:

- Concomitant medications (medication reconciliation)
- Medical history and concurrent illnesses

Also, the following procedures and assessments will be performed:

- Vital signs
- Physical exam (if not obtained at the Screening Visit)
- Lactic acid
- CBC (if not obtained at the Screening Visit) and an optional DNA blood sample
- Serum Pregnancy test
- Dual Energy x-ray absorptiometry (DEXA)
- If CBC is drawn for screening, it will be counted as entry value at the Baseline Visit.
- CMP (comprehensive metabolic panel fasting state), liver function test, glycated hemoglobin, and lipid panel. If drawn for screening, it will be counted as entry value at the Baseline Visit, otherwise they will be drawn at the baseline visit
- Oral glucose tolerance test (OGTT), Brachial artery Doppler (flow mediated dilation of the brachial artery), pulse wave velocity (PWV), and carotid intima-media thickness (CIMT), as well as an optional laser Doppler flowmetry (LDF)
- Blood samples for research labs including study outcomes (inflammatory markers, oxidative stress marker; endothelial function markers; hormones: insulin, leptin, adiponectin/resistin)
- Urine sample for research labs
- Study drug will be dispensed.
- FACIT Fatigue Scale and CESD-10 Questionnaire

Week 2 Visit: At the Week 2 Visit, the following information will be collected:

- Concomitant medications
- Adverse Events (AEs)

Also, the following procedures and assessments will be performed:

- Vital signs
- Lactic acid
- Metformin level (not to draw if patient still up-titrating)

Week 4 Visit: At the Week 4 Visit, the following information will be collected:

- Concomitant medications
- Adverse Events (AEs)

Also, the following procedures and assessments will be performed:

- Vital signs
- Lactic acid, CMP and liver function

- Study drug will be dispensed.
- Metformin levels

Week 8 Visit: At the Week 8 Visit, the following information will be collected:

- Concomitant medications
- Adverse Events (AEs)

Also, the following procedures and assessments will be performed:

- Vital signs
- Physical exam
- Lactic acid, CMP, CBC and liver function
- Blood samples for research labs including study outcomes (inflammatory markers; oxidative stress marker; endothelial function markers; hormones: insulin, leptin, adiponectin/resistin)
- Urine sample for research labs
- Study drug will be dispensed.

Week 12 Visit: At the Week 12 Visit, the following information will be collected:

- Concomitant medications
- Adverse Events (AEs)

Also, the following procedures and assessments will be performed:

- Vital signs
- Lactic acid, CMP and liver function
- Study drug will be dispensed.

Week 16 Visit: At the Week 16 Visit, the following information will be collected:

- Concomitant medications
- Adverse Events (AEs)

Also, the following procedures and assessments will be performed:

- Vital signs
- Physical exam
- Lactic acid, CBC, CMP, lipid panel and liver function
- Brachial artery Doppler (flow mediated dilation), pulse wave velocity (PWV), and carotid intima-media thickness (CIMT), as well as an optional laser Doppler flowmetry (LDF)
- Blood samples for research labs including study outcomes (inflammatory markers; oxidative stress marker; endothelial function markers; hormones: insulin, leptin, adiponectin/resistin)
- Urine sample for research labs
- FACIT Fatigue Scale and CESD-10 Questionnaire

Early Termination Visit: Subjects who are withdrawn from the study will be asked to come in for end of study assessments. The information collected at this visit, as well as the procedures and assessments, will be the same as the Week 16 Visit.

Follow-up Visit 1 (Week 20): There will be a follow-up visit about 4 weeks after the Treatment Phase. The following information will be collected:

- Concomitant medications
- Adverse Events (AEs)

Also, the following procedures and assessments will be performed:

- Vital signs
- Physical exam

Follow-up Visit 2 which is optional (Week 56): There will be a second follow-up visit after about 1 year from starting the Treatment Phase. This could also be completed over a phone call. The following information will be collected:

- Concomitant medications
- Adverse Events (AEs)

Also, the following procedures and assessments will be performed:

- Vital signs
- Physical exam

Standard Methods (all performed for research purposes only):

Dual-energy x-ray absorptiometry (DEXA): We will use DEXA to measure the truncal fat mass percent. During the procedure, subjects will lie on a bed for 10-15 minutes while a scanner X-rays their body fat, lean muscle, and bone masses.

Oral Glucose Tolerance Test (OGTT): The oral glucose tolerance test will allow us to estimate the body's ability to metabolize (or break down) glucose. A blood sample will be drawn after an overnight 8-hour fast (to measure initial glucose level), then a 75g glucose solution will be administered orally. Four more blood samples will be collected over the next 2 hours (to measure subsequent glucose levels).

Brachial Artery Doppler: The brachial artery Doppler measurement will allow us to evaluate endothelial function (hardening of the medium and large arteries). This will let us know the level of vascular disease (diseases of the blood vessels). This study is not painful and is similar to an ultrasound exam. During the procedure a blood pressure cuff will be placed on the forearm. We will take pictures of the vessel in the arm. We will then pump up the blood pressure cuff. It will remain inflated for 5 minutes. Once released, we will collect more pictures. As an optional procedure, we may then administer a single dose of nitroglycerin (a medicine administered to dilate the vessels) under the tongue. We will take a last set of pictures. Blood pressure will be monitored before giving the nitroglycerin. Taking nitroglycerin is optional. The test can still be performed if nitroglycerin is not taken. This test will take a total of about 45 minutes.

Aortic Pulse Wave Velocity (PWV): This test will show us the stiffness of the arteries. This test will be measured with an ultrasound machine by a member of the research team. This test does not involve any shots, radiation or invasive procedures. This will take about 1 hour. Any arrhythmia or a problem with the rate or rhythm of the heartbeat may not allow participation in this test.

Carotid Intima-media Thickness (CIMT): This test will allow us to estimate the amount of arteriosclerosis (hardening of the medium and large arteries), which is an indication of the level

of vascular disease. This study is not painful and is similar to an ultrasound exam. This test will take about 30 minutes.

Laser Doppler Flowmetry (LDF): This optional test will allow us to estimate blood flow in tissues on a microscopic level. This will let us know the level of vascular disease (diseases of the blood vessels). This study is not painful and is similar to an ultrasound exam. During the procedure a blood pressure cuff will be placed on the forearm. We will take pictures of the vessels in the arm. We will then pump up the blood pressure cuff. It will remain inflated for 4 minutes. Once released, we will collect more pictures. We will also warm a small section of the forearm for 2 minutes. We will collect pictures for about 30 minutes. This test will take a total of about 1 hour.

Safety precautions: In this protocol we have the following safety precautions: 1) We will hold the drug during acute illness. Our temporal stopping criteria are discussed below and will be reinforced at each visit. 2) We will provide patients a 24/7 contact number for questions and concerns. 3) Lactic acid measurements will be obtained with our safety laboratories which will happen at least once a month and as needed.

Temporary stopping criteria:

- Patients needing radio-contrast exposure (RCN) for any reason will have their metformin withheld for 48 hours prior to and after the exposure. Drug will be restarted only after a follow up creatinine has been measured and the value considered by the PI to be at baseline.
- Patients will be instructed to stop the medication if for any reason they think they have an acute illness of any type, acute respiratory infection, gastrointestinal, nausea, vomiting or diarrhea; or if there is the underlying risk of being volume depleted. Patients will be asked to contact the study personnel immediately and the PI will decide and will be responsible as to when it is safe to re-initiate the drug.

Permanent stopping criteria:

A patient will be terminated from the study for any of the following reasons:

- eGFR reaches a value of <30 ml/min per 1.73 m^2 in any of the follow-up laboratory assessments.
- Lactate levels are greater than 3.5 in two measurements.
- There are any adverse events or clinical events that the PI judges increases the risk to the patient.
- If metformin level was above the upper limit even when down titrating.
- There are any signs or symptoms of decline or deterioration of their health status.

Statistical Considerations

Data Analysis Plan

Demographic and baseline characteristics will be summarized descriptively by treatment group. Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage. Univariate comparison of the baseline variables will be performed using a Pearson chi-square for categorical variable and non-parametric Mann-Whitney U for continuous variables.

The percent changes in outcome variables from baseline to 16 weeks between the intervention arm and the placebo arm will be compared using either linear mixed effect model (if repeated measures are present for that biomarker) or using an ANCOVA of change if there are only a baseline value and an end off study value. Both outcome variables and baseline values of the outcome variables will be log-transformed—thus exponential of regression coefficient for the interaction term will indicate relative difference in %change from baseline and 16 weeks between groups when using and ANCOVA of change. Using 8-week or 12-week values in analyses is especially helpful when 16-week measures are missing; thus, patients with missing values can be still included in a regression to achieve intent-to-treat principle. There will be two models: 1)

unadjusted, 2) fully adjusted which will adjust for unbalanced baseline covariates (not balanced by randomization) and for potential confounders (demographics, baseline eGFR [as a continuous variable], baseline visceral fat [as a continuous variable], etc. The number of covariates in the model will be limited to prevent overfitting the model.

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