Feasibility and Efficacy of a Well-Formulated Ketogenic Diet in delaying progression of Polycystic Kidney Disease in patients at risk for Rapid Progression

The Ohio State University

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The Ohio State University Combined Consent to Participate in Research and HIPAA Research Authorization

Study Title:	Feasibility and Efficacy of a Well-Formulated Ketogenic Diet in delaying progression of Polycystic Kidney Disease in patients at risk for Rapid Progression
Principal Investigator:	Rima Kang, MD
Sponsor:	US Department of Defense

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

Key Information About This Study
The following is a short summary to help you decide whether or not to be a part of this study. More detailed information is listed later in this form.

The purpose of this research is to determine if ketogenic diet, a low carbohydrate, high fat, diet that is a healthy, non-invasive intervention, can help slow progression of polycystic kidney disease. You will be required to follow a low-carbohydrate, ketogenic diet for a total of 52 weeks in a study. For the first 6 weeks, you will be provided with three ready-to-eat meals per day, along with ketogenic snacks. Afterward, you will be responsible for preparing your own ketogenic meals. The research team will offer dietary education and personalized support from dieticians to assist you in adhering to the diet. Throughout the study, your glucose and ketone levels will be monitored using a CGM/CKM device. Additionally, you will need to perform daily finger sticks in the morning while in a fasted state. At the beginning and end of the study, you will undergo an investigational magnetic resonance imaging (MRI) to assess total kidney volume, our primary measurement for assessing PKD progression. For each visit, you will be required to go to the Physical Activity and Education

Services (PAES) building on The Ohio State Campus, where you will complete surveys, have your blood pressure measured, provide a urine sample, and undergo a whole-body scan. Each blood draw will require a minor amount of blood (6 mL) at each timepoint, for a total of 18 mL (a little less than 1.5 Tablespoons) during each test session. During this period of time, you will be provided with support, coaching and education by the nutrition team. We know that larger kidney volumes on MRI indicate higher risk for progression in patients with polycystic kidney disease and therefore it is one of the outcomes of the study. Our purpose is to demonstrate that the ketogenic diet slows kidney growth, and we will measure to see if there is any effect on kidney function.

1. Why is this study being done?

Polycystic kidney disease is a kidney disease we know leads to end stage kidney disease, or dialysis. We have used lifestyle factors such as hydration to help slow disease progression but ultimately, the disease inevitably leads to end stage kidney disease. Tolvaptan can be used to slow progression of polycystic kidney disease. But, it requires a lot of monitoring for liver toxicity and it is associated with poor side effects. Our current data provides evidence that larger kidneys and rate in growth of the kidneys increases the risk for the disease to progress quickly. We will use MRI to measure the size of your kidneys because it is currently the best way to measure kidney volumes/size. We know that if we are able to show that a ketogenic dietary intervention can slow the decline in over active kidney function and can slow the growth of the kidneys, this will slow progression of disease. The low carbohydrate, high fat, ketogenic diet is a healthy, non-invasive intervention to study that this associated with minimal to no side effects.

2. How many people will take part in this study?

The number of participants anticipated is 20 with polycystic kidney disease who are not currently prescribed Tolvaptan (due to refusal or inability to take tolvaptan) , insulin, or already on a ketogenic diet.

3. What will happen if I take part in this study?

You will be asked to consume a low-carbohydrate, ketogenic diet for a total of 52 weeks. The study includes 6 weeks of 3 ready-to-eat meals per day along with ketogenic friendly snacks. For the rest of the 52 weeks, you will be no longer be provided meals, meaning you will be asked to conform to a ketogenic diet that you will prepare meals for yourself. You will be provided with dietary education, such as education and personalized support from the research team dietitians. You will be fitted with an adhesive sensor called a continuous glucose/ketone monitor (CGM/CKM) that will tell us your glucose and ketone levels, which are metabolites that your body uses for energy, throughout the study trail which can capture data for up to 2-weeks before needing to be changed. Finger sticks will be taken daily in the morning, by the participant to determine ketone and glucose levels in a fasted state so that our team of dieticians will be able to assist you on sticking to the diet.

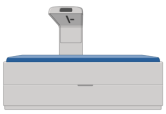
For the first visit and last visits of the study, you will undergo investigational magnetic resonance imaging for assessment of total kidney volume at baseline and 1 year of study

participation. MRI specific safety screening will be performed by a qualified imaging team member prior to the imaging session. This form is important in determining whether you have any reason that you may not have an MRI exam. Women will be given a urine pregnancy test. Only women with a negative pregnancy test will be allowed to participate in the study. You will be asked to remove all metal objects from your body. You will be asked to remove clothing and put on a hospital gown.

MRI uses a powerful magnetic field and radiofrequency waves to make pictures of the inside of your body. Because MRI does not use X-rays, you will not be exposed to any radiation.

You will lie flat on a table that will move into a short, round MRI scanner (somewhat like a tunnel). During the MRI blood pressure will also be measured and monitored. A qualified doctor or nurse will continuously monitor you throughout the exam. These visits should take no longer than 1-2 hours.

Then you will be asked to meet for testing at the PAES building (305 Annie and John Glenn Avenue, Columbus, OH 43210). You will arrive in the morning after an overnight fast and will be asked to complete the surveys provided followed by testing of resting blood pressure. You will be asked to provide a urine sample to test for hydration status and blood will be drawn after sitting for 10-minutes to assess for different analytes. You will also be asked to complete body composition scan (iDXA, Lunar Corporation, Madison, WI) to determine the amount of body fat and lean mass you have. The total time for this visit will be approximately 1-2 hours. You will also complete an online 24-hour dietary assessment tool (ASA24®) and a food frequency questionnaire (DHQIII). We plan to incorporate the use of a novel, continuous glucose, and ketone monitoring (CGM/CKM) sensor developed by Abbott Biowearables. The sensor is applied to the back of the arm where it will continuously measure your glucose and ketones. The sensor is worn for a period of 2-wk. The first sensor will be inserted with assistance from the study team after familiarization. A new sensor will be applied at visit 3 and visit 6. The sensor will always be removed after the end of each intervention. You will be given written instructions on how to remove and dispose of monitor.



i*DXA:* Your muscle mass, fat mass, and bone density will be analyzed using a non-invasive x-ray procedure. For 7 minutes you will be scanned from head to toe by a licensed technician who will provide in-depth information about your body composition changes pre- to post-diet.

Continuous Glucose/Ketone Monitoring

We plan to incorporate the use of a novel, continuous glucose, and ketone monitoring (CGM/CKM) system developed by Abbott Biowearables. The sensor is a patch that is applied to the back of the arm where it will continuously measure your glucose and ketones. The sensor is worn for a period of 2-weeks (Baseline, Week 6 and Month 12). The first sensor will be applied with assistance from the study team after familiarization and will be worn through the first two weeks of the diet. You will be given written instructions on how to remove and dispose of monitor.

You will return to PAES building at Week 6, Month 3, Month 6, Month 9 for another blood draw, body composition test, and 24 hour diet recall. You will return to Martha Morehouse for your 12 Month imagine scan then return to the PAES building for your final blood draw, body composition and 24 hour diet recall. After this testing is complete, you will receive your payment for completing the study.

Study Schedule

	Baseline	Week 6	Month 3	Month 6	Month 9	Month 12
Consent[1]	X					X
Medical History Questionnaire[1]	X	X	X	X	X	X
Vitals and Physical[1] Exam	X	X	X	X	X	X
MRI Scanning[2]	X					X
Blood Draw[3]	X	X	X	X	X	X
Body Composition (DXA)[3]	X			X		X
ASA24®[3]	X	X	X	X	X	X
CGM/CKM	X	X	X	X	X	X

[1] These tests will be done in during your typical appointment in the nephrology department at OSU Wexner Medical Center with your doctor.
[2] The MR Imaging Scans will take place at Martha Morehouse.
[3] These tests will be completed in the Physical Activity and Education Services building on Ohio State Campus and will require morning testing before you have had something to eat.

Analysis
All the blood we collect from you will be kept in a cold storage freezer in our biochemistry lab. Your samples will be labeled with your subject identifier and not your name to maintain confidentiality. We will be measuring several markers in your blood related to metabolism and cardiometabolic response. However, since we will be storing your blood for up to five years, we may think of other markers to measure that we did not think of prior to the start of this study. Any future analysis that we may conduct will be related to this current study only and will not be used for any other research study. You have the right to decline the use of your samples for

any potential future analysis. Below are two check boxes indicating that you either will allow us or will not allow us to use your blood to measure future markers. If you select not to allow us to use your blood for future tests, then any leftover samples will be destroyed. Please select an option below and sign your name with today's date. The extra signature indicates that you have thought about, read and understand this option. Please keep in mind that the selection of either option will have no impact or penalty during your participation in the study, and you will not lose any benefits to which you are otherwise entitled.

____ **Yes**, I give permission to use my blood samples for any future analysis.

____ **No**, I do not give permission to use my blood samples for any future analysis.

Your Signature: _____

Today's Date: _____

4. How long will I be in the study?

Your involvement in the study will be over the course of one year. At the start of the study, your time involvement will be most extensive during the initial visit. This will include time to register for the MRI and get the scan done. At the beginning of the dietary intervention portion of the study (the initial visit), you will arrive at the PAES building the morning after an overnight fast. You will then be tested for hydration, your height and body mass will also be measured. At this visit, you will have your blood pressure checked, along with blood and urine tests. The blood we collect will be stored for 5 years. You will also have a fingerstick blood test done, and your body composition checked by a dual-energy x-ray absorptiometry (DXA). The total time for the first visit will likely be from 1-2 hours. Visits 2-5 will involve similar testing, except no MRI or DXA scan will be done. The third visit will be similar to the first with regard to testing. Each individual may have different time involvement depending on how much coaching is required for the dietary changes.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

Ketogenic Diet Intervention:

There are no significant risks associated with consuming a well-formulated ketogenic diet. In our prior research we have assessed thousands of metabolic panels in patients assigned to ketogenic diets. Abnormal responses are rare, but it is expected that there will be modest changes in some blood markers. These markers are expected to remain within normal limits and not pose a serious concern. Nutritional ketosis is associated

with natriuresis (increased loss of sodium in the urine) and fluid loss. If the extra sodium excreted is not compensated for in the diet, the subsequent contracted plasma volume can manifest in side effects and adrenal stress including a hormonal response that disrupts body mineral status. Our diets contain adequate sodium and potassium to ensure mineral nutriture. The diet intervention may be challenging for participants since it will require them to limit foods they are accustomed to eating. Participants will be made aware of the general dietary requirements including lists of foods they will need to restrict (as well as foods that will be permitted) during the informational session, so they can make an educated decision to participate. In our plan to watch over how the diet is going for you, we really care about how you feel. If the special food plan we give you causes any tummy troubles or other problems, we want to know right away. You'll be talking to a nutritionist regularly, and they'll help you figure out what might be causing any issues. We'll also have you check your blood ketone levels every day to catch any problems early. Plus, you'll tell us about your meals in short and longer reports, so we can see if certain foods might be causing any feelings you don't like. Our main goal is to make sure you feel good while trying this diet, and if there are any bumps in the road, we're here to help you through them!

MR Imaging:

MRI is considered minimal risk procedure, and is standard of care. The static magnetic fields can exert forces on magnetic objects and induct electric currents in any conductive material. The main risks would be dislodgement or malfunction of medical implants or metallic foreign objects, or current induction in tissue and alteration in physiologic function. Therefore, any potential participants with bioimplants, pacemakers, cerebral aneurysm clips will be excluded from the study. The MRI device makes a loud noise, which may cause some discomfort. Additionally, subjects may feel closed in during the MRI scan if they are claustrophobic.

Finger-stick Testing:

The finger stick may cause a slight immediate discomfort at the specific stick site. Under normal conditions, there are minimal risks to you when performing finger-sticks that include: bruising; light-headedness or dizziness due to fear of needles; and infection.

Venous Blood Draws:

The venous blood draw will occur three times during each study session, meaning we will obtain blood with a small needle four separate times. Each blood draw will require a minor amount of blood (6 mL) at each timepoint, for a total of 18 mL (a little less than 1.5 Tablespoons) during each test session. Under normal conditions, there is no risk of harm from this minor amount of blood drawn. A trained and certified phlebotomist will perform the blood draw and will be responsible for each blood draw. The site of the blood draw may cause slight immediate pain or discomfort at the entry site. Other risks include bruising, light-headedness or dizziness due to fear of needles, and infection.

Continuous Ketone/Glucose Monitor:

The patch application may cause a slight immediate discomfort at the specific stick site. Under normal conditions, there are minimal risks to you when performing application that include: bruising; burning; soreness, hypersensitivity, itching, redness, pain that the insertion site, subcutaneous hemorrhaging, light-headedness or dizziness due to fear of needles; and infection.

Exclusion of Tolvaptan:
We will only enroll you if you are not able or refuse to take If you are currently being treated with Tolvaptan will be excluded from the study. However, Tolvaptan is associated with significant effects that increase how frequently you urinate but may not assist with what you get rid of in your urine. Tolvaptan, a vasopressin V2 antagonist, is the only US Food and Drug Administration (FDA) approved drug for slowing progression of PKD in individuals at risk for rapid progression. However, Tolvaptan is associated with significant effects that increase how frequently you urinate but may not assist with what you get rid of in your urine.

7. What benefits can I expect from being in the study?

You may benefit from individualized coaching for an intervention that may slow progression of polycystic kidney disease. It is minimally invasive and minimal side effects noted. In the long-term, we hope to gain more knowledge from blood and urine testing that may shed light on new therapeutic targets. If you have not been recommended to take Tolvaptan or chose not to take it, the metabolic effects of a ketogenic diet may positively impact your PKD.

8. What other choices do I have if I do not take part in the study?

If you choose not to participate, then you continue your standard of care treatment as usual. You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

9. What are the costs of taking part in this study?

The participants are expected to purchase and prepare their own food for the dietary intervention (ketogenic diet) after week 6 of the study. The imaging, blood, and urine studies are covered costs for patients enrolled in the study.

10. Will I be paid for taking part in this study?

You will be paid $100 in the form of a check after completing the testing day at week 6, and another $100 in the form of a check after each testing session for a total of $500 for completion of the entire study. By law, payments to participants are considered taxable income.

11. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of research participants.

13. Will my de-identified information (and bio-specimens) be used or shared for future research?

Yes. Your blood will be saved for future analysis for biomarkers that may identify targets for new therapies.

14. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

15. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and present medical records;
- Research records;
- Records about phone calls made as part of this research;
- Records about your study visits;
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual;
- Information gathered for this research about:
  Physical exams
  Laboratory, x-ray, and other test results

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office record.

IV. Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported; and
- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and

- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your authorization will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

Your health information will be protected and stored in a safe area where unintended individuals will not be able to gain access.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

16. Who can answer my questions about the study?

For questions, concerns, or complaints about the study, or if you feel you have been harmed as a result of study participation, you may contact the nephrology office at (614) 293-4055.

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact the HIPAA Privacy Officer at (614) 293-4477.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact Rebekah Varner in our nephrology office at (614) 293-4055.

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of participant	**Signature of participant**
	AM/PM
	Date and time
Printed name of person authorized to consent for participant (when applicable)	**Signature of person authorized to consent for participant (when applicable)**
	AM/PM
Relationship to the participant	**Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time