The University of Texas Southwestern Medical Center
Parkland Health & Hospital System
Children's Medical Center
Retina Foundation of the Southwest
Texas Scottish Rite Hospital for Children
Texas Health Presbyterian Hospital Dallas

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research:	Preventing metabolic side effects of thiazide diuretics with KMgCitrate
Funding:	Center for Mineral Metabolism and Clinical Research
Study Doctors:	Wanpen Vongpatanasin

You may call these study doctors or research personnel during regular office hours at 214-648-2968. At other times, you may call them at 214-645-8424.

Instructions:
Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?
This study is being done to test if potassium magnesium citrate powder (KMgCit) is more effective than potassium chloride (KCl) in preventing increases in blood sugar and insulin levels which are side effects of Chlorthalidone. Chlorthalidone is a commonly used diuretic approved for the treatment of high blood pressure.

Why is this considered research?
This is a research study because potassium or magnesium supplements are not approved preventing the increase in blood sugar and insulin caused by Chlorthalidone.

The following definitions may help you understand this study:

- Double-blind means neither you nor the researchers will know which drug you are receiving.
- Randomization means you will be placed by chance (like a flip of a coin) in one of the study groups.

- Standard medical care means the regular care you would receive from your personal doctor if you choose not to participate in this research
- MAGNETIC RESONANCE IMAGING OR MRI: A method to take pictures or measure metabolism of the inside of the body. The MRI exam in this research is investigational.
- TESLA: is the unit for magnetic field strength. Standard clinical MRI scans are typically performed between 1 and 3 Tesla. We will use 3 Tesla to measure fat in your liver and 7 Tesla to measure your muscle magnesium. The 7 Tesla MRI procedures for this study will be done on a research scanner.
- Researchers means the study doctor and research personnel at the University of Texas Southwestern Medical Center in Dallas and its affiliated hospitals.

Why am I being asked to take part in this research study?
You are being asked to take part in this study because you have high blood pressure (blood pressure on or off treatment is between 130/80and 160/100).

Do I have to take part in this research study?
No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at this center.

How many people will take part in this study?
About 72 people will take part in this study at UT Southwestern.

What is involved in the study?
If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures. Some of the procedures may be part of your standard medical care, but others are being done solely for the purpose of this study.

<u>Screening Procedures</u>

To help decide if you qualify to be in this study, you will have the following tests and/or evaluations.

- Physical exam, medical and surgical history, history of mental illness, and substance abuse,
- Vital signs,
- Demographic information (age, sex, ethnic origin),
- If you are taking medications for high blood pressure, you will be asked to stop taking your current medications.

<u>Group Assignment</u>

If the researchers believe you can take part in this study, you will be given chlorthalidone for 2 or 3 weeks. Then you will be asked to take either potassium magnesium citrate or potassium chloride supplement twice a day for 4 months. The supplement will be provided in the powder form and you will need to dissolve each packet in the drinking water before taking it. You have a 1 in 2 chance of receiving either of the potassium supplements.

Neither you nor the researchers will be allowed to choose which group you are placed into.

Neither you nor the researchers will know which group you are in. However, the sponsor will release the information about your assignment to the researchers if it is needed for your safety.

Study Medication/Intervention

If you decide to participate in this study, you will be asked to

- Stop current medications (if taken) for hypertension for 3 weeks
- Take Chlorthalidone daily alone for 2 or 3 weeks. Then you will;
- Take Chlorthalidone daily AND
- Take 1 package of Potassium Chloride powder, dissolved in water twice a day(with breakfast and dinner) for 4 months

or

- Take 1 package of Potassium Magnesium Citrate powder, dissolved in water twice a day (with breakfast and dinner) for 4 months

The blood, urine, and imaging tests in this study are designed for research and not for medical purposes. These tests are not useful for finding problems or diseases. Even though the researchers are not looking at your blood or urine tests to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or treatment. Because the blood and urine tests done in this study are not for medical purposes, the research results will not be sent to you or to your regular doctor.

Procedures and Evaluations during the Research

You will be asked to come in for 6 visits. All Procedures during this study are for experimental purposes. If you have a history of claustrophobia or a metal device that precludes MRI, you will not have an MRI done as a part of the study.

Visit 1: (At 0 week)

- Research personnel will check your blood pressure and your weight.
- You will be asked to collect urine for 24 hour urine
- Urine pregnancy test will be done for women of child bearing age
- Research personnel will collect three tablespoons of blood from the tube in your arm for the research purpose.
- You will be asked about any symptoms of stomach or intestinal discomfort,

nausea, or heartburn, you might have before taking study medications.

- You will be given a stool card kit which you will need to return prior to your next visit.
- If you were taking blood pressure medication, you will be asked to stop your blood pressure medications for 3 weeks.
- Research personnel will provide counseling regarding low sodium diet and diet rich in fruits and vegetables or DASH diet to control blood pressure
- If you were not taking blood pressure medication, you will have MRI (Magnetic Resonance Imaging) of right calf for measurement of magnesium content and MRI of your liver to measure fat content for research purposes
- Women of child bearing age will have a urine pregnancy test
- You will then start taking Chlorthalidone 25mg daily if you were not on blood pressure medications before the study

Visit 2 (1 week after drug washout)

- Research personnel will check your blood pressure.
- If blood pressure is 160/100 or above, we will start Chlorthalidone 25 mg without delay. If your blood pressure is under 160/100 mmHg, you will return in one week.
- Research personnel will provide counseling regarding low sodium diet and diet rich in fruits and vegetables or DASH diet to control blood pressure

Visit 3 (2 weeks after drug washout)

- Research personnel will check your blood pressure.
- If blood pressure is 160/100 or above, we will start Chlorthalidone 25 mg without delay. Patient with blood pressure under 160/100 mmHg will return in one week.

Visit 4: (3 weeks after drug washout)

- Research personnel will check your blood pressure.
- You will have MRI (Magnetic Resonance Imaging) of right calf for measurement of magnesium content and MRI of your liver to measure fat content for research purposes
- You will start taking Chlorthalidone 25 mg daily

Visit 5: (2 weeks after the first study medication)

- Research personnel will check your blood pressure and your weight and count your pills. If your blood pressure is less than 90/60 dose of chlorthalidone will be reduced by half and blood pressure will be checked in 1 week. If your blood pressure is greater than130/80, you will be asked to take amlodipine 5mg daily
- Research personnel will collect three tablespoons of blood from the tube in

your arm for the research purpose.
- You will be asked to collect urine for 24 hour urine
- You will be asked about any symptoms of stomach or intestinal discomfort, nausea, or heartburn, you might have after taking study medications.
- If your potassium level is less than 3.5 mEq/L, you will go directly to visit 4 and skip visit 3.

Visit 6: (those on Chlorthalidone for 3 weeks)
- When you return urine sample, research personnel will check your blood pressure and your weight. If your blood pressure is below 120/80, you will be excluded from the study. If your blood pressure is above or equal to 120/80, you will be able asked to take 25mg of chlorthalidone daily.
- Research Personnel will count Chlorthlidone pills
- You will be asked about any symptoms of stomach or intestinal discomfort, nausea, or heartburn, you might have before taking study medications.
- You will be given either potassium magnesium citrate OR potassium chloride

Visit 7: (1 month on Chlorthalidone plus KMgCit OR KCl)
- Research personnel will check your blood pressure and your weight and count your medication packages and pills
- If your blood pressure is greater than130/80, you will be asked to take amlodipine 10mg daily
- Research personnel will check fasting glucose level for research purpose.
- You will be asked about any symptoms of stomach or intestinal discomfort, nausea, or heartburn, you might have after taking study medications.

Visit 8: (2 months on Chlorthalidone plus KMgCit OR KCl)
- Research personnel will check your blood pressure and your weight and count your medication packages.
- If your blood pressure is greater than130/80, you will be asked to take doxazosin 2mg daily
- Research personnel will collect three tablespoons of blood from the tube in your arm for the research purpose.
- You will be asked to collect urine for 24 hour urine
- You will be asked about any symptoms of stomach or intestinal discomfort, nausea, or heartburn, you might have after taking study medications.
- You will be given a stool card kit which you will need to return prior to your next visit.

Visit 9: (3 months on Chlorthalidone plus KMgCit OR KCl)
- Research personnel will check your blood pressure and your weight and count your medication packages

- If your blood pressure is greater than130/80, you will be asked to take doxazosin 4mg daily
- Research personnel will check fasting glucose level for research purpose.
- You will be asked about any symptoms of stomach or intestinal discomfort, nausea, or heartburn, you might have before taking study medications.

Visit 10: (4 month on Chlorthalidone plus KMgCit OR KCl)

- Research personnel will check your blood pressure and your weight and count your medication packages and pills
- You will be asked to collect urine for 24 hour urine
- Research personnel will collect three tablespoons of blood from the tube in your arm for the research purpose.
- You will be asked about any symptoms of stomach or intestinal discomfort, nausea, or heartburn, you might have before taking study medications.
- You will be given a stool card kit which you will need to return to us
- You will have MRI of right calf and MRI of your liver for research purposes. End of study

You will have magnetic resonance imaging (MRI) of your liver and calf. For this procedure, you will lie quietly inside a large, doughnut-shaped magnet for about 30 minutes.

How long can I expect to be in this study?
The study will last for approximately 18-19 weeks. Follow up visits with MRI will take about 3 hours. Visits without imaging will take about 60 minutes

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?

Study Procedure/Intervention
Because of your participation in this study, you are at risk for the following side effects. You should discuss these with the researchers and your regular health care provider.

a) Chlorthalidone: Information about known problems is based upon the experiences of hypertensive patients on treatment for 4-5 years.
• In past research, 12 out of 100 users of chlorthalidone had diabetes mellitus, whereas 8-10 out of 100 users of other blood pressure medications had diabetes mellitus
• 9 out of 100 had low potassium
• 1 out of 100 had gout
• Risk of kidney failure is not increased compared to other blood pressure medication. However, patients who cannot drink normal amount of fluid or maintain normal amount of salt intake may have low blood pressure, dehydration, and kidney problem

b) Potassium Chloride powder and Potassium Magnesium Citrate powder: may cause some, all or none of the side-effects listed below.

	Frequent 30% of subjects	Occasional 15% of subjects	Rare Less than 1% of subjects
Serious			High potassium levels in your blood
Less Serious		Stomach upset, vomiting, nausea, belching, diarrhea, loose bowel, stomach or intestinal pain, loss of appetite, pain with swallowing,	
Minor			Fatigue

c) Amlodipine may cause some, all or none of the side-effects listed below;

	Frequent 30% of subjects	Occasional 15% of subjects	Rare Less than 1% of subjects
Serious			Allergic reaction
Less Serious		Swelling of the feet, constipation, headache, elevated heart rate, heart pounding	Low blood pressure, dizziness
Minor			Increase in size of gums

d) Doxazosin may cause some, all or none of the side-effects listed below

	Frequent 30% of subjects	Occasional 15% of subjects	Rare Less than 1% of subjects
Serious			Allergic reaction
Less Serious	Headache	Confusion, dizziness, faintness when getting up from a lying or sitting position, sweating, swelling in legs,	

		elevated heart rate, heart pounding	
Minor			Frequent urge to urinate

e) MRI: There are no known risks from exposure to magnetic fields. You may experience nervousness and/or anxiety due to the loud banging made by the machine while it is taking pictures and from confinement in a tight space (claustrophobia). If you become anxious, you can stop the procedure at any time .You may also experience some discomfort and fatigue from lying still during imaging. If you have any metal clips or plates in your body, you should tell the investigator. MRI may not be appropriate if you are pregnant or are trying to become pregnant. MRI may not be appropriate if you have permanent eyeliner or eyebrows or any pieces of metal in your body, such as the following:

- Heart pacemaker, heart valve replacement, or aortic clips
- Metal fragments in your eyes, skin, or elsewhere in your body
- Brain clips or pieces of metal used in aneurysm surgery or intracranial bypass
- Venous umbrella
- Pieces of metal in the body resulting from work as a sheet-metal worker or welder
- Clips placed in an internal organ
- Prosthetic devices, such as middle ear, eye, joint, or penile implants
- Joint replacement.
- Hearing aid that cannot be removed
- Neurostimulator
- Insulin pump
- Intrauterine device (IUD)
- Shunts or stents
- Metal mesh or coil implants
- Metal plate, pin, screws, or wires, or any other metal implants

Please tell the researchers if you have any metal in your body as this will exclude you from completing the MRI portion of the study

<u>Risk of High Field MRI</u>

7T MRI Scanner: 7T scanners are solely for research purposes for measuring magnesium in your muscle and are considered experimental (i.e not used for clinical diagnosis). The FDA has concluded that MRI systems operating at 7 Tesla do not represent significant risk. However, this research study will expose you to strong magnetic fields and long term safety data is limited. At this time, there are no known long-term risks of exposure to 7 Tesla magnetic fields.

3T MRI Scanner: The 3T scanner used in this study is for measurement of fat in your liver. It has been approved and is used in clinical diagnosis.

-Blood pressure cuff inflation: The blood pressure cuff will squeeze your arm tightly. However, any discomfort will stop as soon as the pressure in the cuff is released.

-Blood samples: You may experience discomfort, bleeding, and/or bruising. You may feel dizzy or faint. On a rare occasion, an infection may develop at the site where the blood was collected.
- Urine Collection: No known risk associated with urine collection.

Loss of Confidentiality
Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks Embryo, Fetus or Breast-fed Infant
If you are part of this study while pregnant or breast-feeding an infant, it is possible that you may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females cannot participate in the study. If you can become pregnant, a urine pregnancy test will be done, and it must be negative before you participate in this study. If you do become or are planning to become pregnant during this study, you must tell the researchers immediately

Risks of Blood Drawing
Risks associated with drawing blood from your arm include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible, although unlikely.

You will have 12 tablespoons (180 ml) of blood collected over 4.5 months because you are in this research study.

Other Risks
There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?
The research laboratory is fully equipped to handle any untoward side effects. Dr. Vongpatanasin is a hypertension specialist and cardiologist with extensive experiences in performing the research procedures in this study. Emergency equipment, in the event of that your heart stops or you stop breathing, is immediately available with highly trained staff.

What will my responsibilities be during the study?

While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Report to the researchers any injury or an illness while you are on study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?
If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking, including any medications you are taking for this study.

What are the possible benefits of this study?

If you agree to take part in this study, there will not be direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research.

We hope the information learned from this study will benefit others with high blood pressure in the future. Information gained from this research could lead to better treatment of hypertension.

What options are available if I decide not to take part in this research study?
You do not have to participate in this research to receive care for high blood pressure. Instead of being in this study, you can receive high blood pressure treatment from your regular doctor.

Will I be paid if I take part in this research study?

Yes. You will be issued a UT Southwestern Greenphire ClinCard, which can be used as a credit or debit card. You will be paid $1,000 at the end of this 4.5 - 5 month study with MRI. You will be paid $800 at the end of this 4.5 – 5 month study if MRI's are not completed. If you stop taking part in this study or are withdrawn by the research team, you will be paid according to the number of weeks you participated in the study at $55 per week (if you were not on blood pressure medications before the study and complete MRI) or $47 per week (if you were on blood pressure medications before the study and complete MRI). If you are unable to complete the MRI's as a part of the study related to medical device or claustrophobia, you will be paid according to the number of weeks you participated in the study at $44 per week (if you were not on blood pressure medications before the study) or $38 per week (if you were on blood pressure medications before the study).

There are funds available to pay for parking expenses at the Aston Clinical Building. There are no funds available for transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

Your name, address, date of birth and social security number will be shared with a third-party solely for the purposes of compensation processing. All information will be stored in a secure fashion.

Please note that if you are on record as owing money to the State of Texas, such as for back child support or a delinquent student loan, the payment may be applied to that debt.

An IRS Form 1099 will be sent to you if your total payments are $600 or more in a calendar year, unless it's a reimbursement.

Will my insurance provider or I be charged for the costs of any part of this research study?
No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Medications, Labs, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas.

You retain your legal rights during your participation in this research

Can I stop taking part in this research study?

Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

Your doctor is a research investigator in this study. S/he is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

If I agree to take part in this research study, can I be removed from the study without my consent?

Yes. The researchers may decide to take you off this study if:

- Your medical problem becomes worse.
- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?

Information about you that is collected for this research study will remain confidential unless you give your permission to share it with others, or as described below. You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people; and
- The UT Southwestern Institutional Review Board.
- Quest Diagnostic and Aston Clinical Laboratory

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Whom do I call if I have questions or problems?

For questions about the study, contact Dr. Vongpatanasin 214-648-3180 during regular business hours and at 214-645-8000 after hours and on weekends or holidays.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.
- You understand that a copy of this signed consent document, information about this study, and the results of any test or procedure that may affect your medical care, may be included in your medical record. Information in your medical record will be available to health care providers and authorized persons including your insurance company.

_____

Name of Participant (Printed)

_____ _____ _____ AM / PM

Signature of Participant Date Time

_____

Name of Person Obtaining Consent (Printed)

_____ _____ _____ AM / PM

Signature of Person Obtaining Consent Date Time

Interpreter Statement:

I have interpreted this consent form into a language understandable to the participant and the participant has agreed to participate as indicated by their signature on the associated short form.

_____

Name of Interpreter (Printed)

_____ _____ _____ AM / PM

Signature of Interpreter Date Time