ADOLESCENT ASSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: The impact of phosphate metabolism on healthy aging Part 1: Determine the association between duration and dose of treatment with phosphate supplement and renal, vascular, and cardiovascular function; and Part 2: Determine the impact of short-term phosphate supplementation on blood and urine markers of cardiovascular, lipid, renal and mineral metabolism in HHRH and XLH

Principal Investigator (the person who is responsible for this research): Clemens Bergwitz, M.D. – 300 Cedar Street, TAC S117, New Haven, CT 06520

Funding Source (who pays for the study): This study is funded by the National Institutes of Health through a grant to Yale University.

Why am I here?

- We are asking you to join a research study.
- We want to find out if phosphate (what you are getting as part of your treatment) can cause health problems as people get older. The study will look at how kidneys and the heart work in people with conditions like yours after getting phosphate for a long time.
- This form explains the research study and your part in the study.
- Please read it carefully. Take as much time as you need.
- Please ask the study staff questions about anything you do not understand.
- You can ask questions now or anytime during the study.
- If you join the study, you can change your mind later.
- You can quit the study at any time.
- We will also ask your parents to allow you to be in the study.

We plan to study 30 participants (grown-ups and children) with two different conditions: Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH), and X-linked hypophosphatemia (XLH).

APPROVED BY THE YALE UNIVERSITY IRB 7/20/2021

What will happen during the study?

If you agree to be in this study, we will first look into your medical records to see how your kidneys and heart are working. We will write down information about treatments you have been getting and how long they lasted. We will continue to check your medical records for 5 years after the study is over to see if there is any new information entered by your doctor.

Next, we will ask you to stop taking your phosphate and/or calcitriol for 2 weeks. Stopping vitamin D and phosphate supplements can lead to the bone pain and muscle weakness you experienced before you began therapy. However, a short period of two weeks has been safe in similar studies. If you feel bone pain or muscle weakness, we will ask you parents to have your blood phosphate levels tested. If your blood phosphate level drops below a safe level (2.0 mg/dl), we will ask you to restart phosphate supplements.

After two weeks without phosphate or calcitriol, we will we will ask your parents to bring you to the YNHH Hospital Research Unit (HRU) to have the tests listed below. If you have had some of these tests before, we may ask your doctor to share the results and you will not have to repeat them. The study visit will start in the morning, and you will not stay overnight.

- We will **ask you questions** about your health and food that you eat.
- We will do a **physical exam**, just like the one you get when you see your doctor.
- We will ask you to not eat anything for 12 hours and come to the visit without eating anything in the morning. We will **draw your blood** and ask you to pee in a cup so that we can **test your urine**. The total amount of blood drawn in this study will be approximately 30 cc (about an ounce) at that visit.
- If you are a girl and you started your period, we will ask you to have **a pregnancy test** before you start this study. Only you will be told the results. If you are pregnant, we will also advise you to get care for your pregnancy. You will be asked not to be in the study or you will be removed from the study, if your pregnancy test is positive. You need to know that your parents may ask you why you cannot be in the study or why you were asked to leave the study. If there is any chance that you are pregnant or you might become pregnant during the time of this study, we would recommend that you think really carefully about whether you should be in the study. It is okay if you decide that you do not want to be in the study or to stay in this study. You do not need to give a reason for not being in the study.
- We will do a **renal ultrasound** test to see how your kidneys work. The test uses sound waves to show a picture of the inside of your body. It does not use radiation and it does not hurt. You will lie on your belly

and you will be told when to move so that we can get a different picture of the kidney. The technologist will put a clear gel on the skin over the area to be looked at. The technologist will press the probe against the skin and move it over the area being studied. Once the test is done, the technologist will wipe off the gel. Let the technician know if you are not comfortable.

- You will undergo a test called **a Standard Transthoracic Echocardiogram** (TTE), which checks for problems with your heart. The test sends sound waves through a small device placed on your chest and it does not hurt. The sound waves show how your heart works on a monitor. You will lie on your back or left side. A doctor or a nurse will place gel on your chest and move a probe back and forth on your chest to look at your heart. You will need to lie still during the test. You may be told to hold your breath at times, or to breathe slowly.
- You will do a test called a **peripheral arterial tonometry (PAT).** PAT checks how your blood flows through your body. It does not hurt. We will ask you to not smoke, drink any drinks with caffeine, or eat for 12 hours before the PAT test. You will lie on your back with a finger probe on the index finger of each hand and a pressure cuff on one upper arm in a quiet room. The PAT test will record signals from your body for 10 minutes. Then, we will pump up the blood pressure cuff on your arm for 5 minutes. After that, the PAT will record signals from your body for additional 10 minutes.

After the 1st study visit, we will start a four-week phosphate supplementation period. We will ask you to take a certain amount of phosphate supplements, either as KPhos 250 mg tablets or as a liquid you will drink. We will calculate the amount of phosphate supplement based on your food intake so that the total amount of phosphate you take in each day is about 3,500 mg, considering both your food intake and the supplements. You will start with a small amount of supplement and increase the amount every day for six days in order to avoid getting an upset stomach. After the sixth day, you will stay at the same level of supplement for the rest of the four-week period.

At the end of the four-week supplementation period, we will ask you to return to the Hospital Research Unit for a second study visit, where you will have these tests:

- We will do a **physical exam**, just like we did at the first study visit.
- We will ask you to not eat anything for 12 hours and come in without eating anything in the morning. We will **draw your blood** and ask you to pee in a cup so that we can do a **urine test**. The total amount of blood drawn in this visit will be approximately 30 cc (about an ounce).

- We will repeat the **peripheral arterial tonometry (PAT) test.** It will be just like the PAT test from the first study visit.

If we find out important new information while you are participating in the study that could change your mind about participating, we will let you know.

What are the possible risks of the study?

Stopping vitamin D and phosphate supplements can lead to the bone pain and muscle weakness you experienced before you began therapy. However, a short period of two weeks has been safe in similar studies. If you feel bone pain or muscle weakness, we will ask your parents to have your blood phosphate levels tested. If your blood phosphate level drops below a safe level (2.0 mg/dl), we will ask you to restart phosphate supplements.

There is some discomfort associated with blood draws and injections such as a slight risk of bleeding, bruising, or infections at the needle sites. Some patients experience dizziness or even fainting with injections or blood draws. If you would like, we can use EMLA® cream to make your skin numb for the blood draw.

Sometimes patients experience side effects related to phosphate supplementation. These can include upset stomach, vomiting, diarrhea, dizziness, headache, aching in the bones or joints, muscle cramps, and stomach pain. Rarely these other very serious side effects can happen: confusion, fast or irregular heartbeat, unusual weakness, tingling or numbness in the hands or feet, and a change in the amount of urine produced. If you experience any of these symptoms, you or your parents should notify the study doctor or study staff as soon as possible. You may remain on the study, but we would reduce the amount of phosphate supplementation, or you can remove yourself from the study. Another rare side effect is an allergic reaction to the drug, which may cause a rash, itching or swelling, especially itching or swelling in the face, tongue or throat, severe dizziness, or trouble breathing. If you have an allergic reaction, we would ask you to stop taking the study drug.

What are the possible benefits of the study?

This is not a treatment study and you will not benefit directly. If you take part in this study, other people with XLH or HHRH may be helped in the future.

Will it cost any money for me to be in the study?

Neither you nor your parents will have to pay for the tests that are done for research purposes only.

Your parents or their insurance will have to pay if we do routine care tests (tests that you would have even if you were not taking part in this study). They may also have to pay any deductibles or co-pays. If you or your parents have any questions about any costs, please speak with the study doctors and study staff. If you or your parents have any questions about any costs, please let us know. We can ask somebody from the Patient Financial Services to talk to you about these costs.

Alternatives

You are not required to take part in this study. You may talk with your usual doctor about the possibility of obtaining additional clinical tests without participating in this study.

How do you protect my information?

If you decide to take part in this research study, you will be required to give us information about your substance use. We will also collect genetic information. We obtained a document called a Certificate of Confidentiality (CoC) from the National Institutes of Health. With this Certificate, we may not share information, documents, or your samples such as blood or urine (biospecimens) that may identify you in any court proceeding, even if there is a court subpoena. Information, documents, or biospecimens protected by this Certificate cannot be given out to anyone else who is not connected with the research unless you agree to it, for example to be used for your medical treatment. However, there are some situations when we have to let somebody else know if we think that you may harm yourself or others, if somebody else can harm you, or if you have any reportable diseases (such as HIV or Hepatitis). We can also share your information with other researchers to do other research projects, if it is allowed by regulations protecting research participants.

Even when a Certificate of Confidentiality is in place, you and your family members must still continue to actively protect your own privacy. If you give your written permission for anyone to receive information about your participation in the research, then we may not use the Certificate of Confidentiality to withhold this information.

Let us know if you have any questions about the Certificate of Confidentiality.

We are serious about protecting your confidentiality. We will store all of your research records in locked cabinets and secure computer files. We will not place your name on any research data. Instead, we will label your information with a code number. The master list that links your name to your code number will be stored in a different secure place. We will keep that list forever. We will also keep all other study data as long as we need it.

We will enter results of tests that you would do even if you were not participating in this research in your medical records. Anyone who has access to your medical records will be able to see this information, for example, your doctors or your health insurance company. We will not enter results of the research tests into your medical records.

We will keep all the information you give us confidential. We will not share your study results with anyone unless you agree to it. Your name will not be included in any reports about this study.

A description of this research study 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 findings from the study. You can search this web site at any time.

What Information Will You Collect About Me in this Study?

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The information about your health that will be collected in this study includes:

- The entire research record and any medical records held by Yale New Haven Hospital created at any time starting with when you were born
- Records about phone calls made as part of this research
- Records about your study visits
- Results of the physical exams
- Laboratory, x-ray, and other test results
- Diaries and questionnaires

How will you use and share my information?

We will use your information to conduct the study described in this form.

We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies

- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about potassium and sodium phosphates involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those providers who are participants in the Electronic Medical Record (EMR) system.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator, Clemens Bergwitz, M.D.
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- The Data and Safety Monitoring Board (DSMB) and others authorized to monitor the conduct of the Study.

The research staff at the Yale School of Medicine and Yale-New Haven Hospital have to obey privacy laws and make sure that your information stays confidential. Some of the people or agencies listed above may not have to obey those laws, which means that they do not have to protect your data in the same way that we do. However, to better protect your health information, we have agreements with these individuals or companies that require that they keep your information confidential. Let us know if you have questions about this.

Why sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to those who may need it for research purposes.

What if I change my mind?

Your permission to use and give out your health information that we collect when you participate in this study will never expire. However, you may withdraw or take away your permission at any time. You can do it by telling

the study staff or by writing to Clemens Bergwitz, M.D. at Yale University, 300 Cedar Street, TAC S117, New Haven, CT 06520.

If you take away your permission, you will not be able to stay in this study but the care you get from your doctor will not change. We will not collect any new health information about you when you withdraw your permission. However, we can use and share information that has already been collected with others until the end of the research study to make sure the study was done correctly.

What will happen if I get hurt because I joined the study?

If you get hurt when you participate in this study, get treatment and contact the study doctor, Clemens Bergwitz at (203)737-5450 as soon as you can. If you get hurt because you participate in this study, we can provide treatment. However, Yale and Yale-New Haven Hospital cannot pay for that treatment. Your parents or your insurance will be expected to pay the costs. There is no additional financial available compensation for injuries or lost income. You do not give up any of your legal rights by signing this form.

Do I have to be in this study?

No, being in this study is up to you. You can say no now if you already know that you do not want to join the study. You can say yes now and if you change your mind later, you can leave the study at any time. Just tell the study staff that you no longer want to be part of it. The researchers may still use the information they had already collected about you before you withdrew from the study.

There will be no negative consequences regardless of what you decide to do. Your decision will not change the care you receive or benefits that you would normally get.

We would like to contact you in the future if there are other research studies that you may participate in.
Is it OK for us to contact you?

_____YES _____No

What if I have questions?

We have used some difficult words in this form. Please ask about anything you don't understand. Think about the information we gave you for as long as you want to before you make a decision. You can talk to your

family about your decision as well. If you come up with questions later, you can call the study doctor, Clemens Bergwitz, at (203)737-5450.

Authorization and Permission

I have read this form (or someone has read it to me) and I have decided to participate in the project described above. Its general purposes, the things I will do in the study and possible risks and inconveniences have been explained to my satisfaction. My signature also shows that I have been given a copy of this assent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the reasons described in this form. If I decide not to give permission, I understand that I will not be able to be in this research.

Name of Participant: _____

Signature: _____

Date: _____

_____ _____

Signature of Person Obtaining Assent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Clemens Bergwitz, M.D. at (203)737-5450. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203)785-4688.