Zinc Supplementation and Cardiovascular Risk in HIV

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UNIVERSITY HOSPITALS CASE MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v. 11.2012)

Project Title: Pilot Study of Zinc Supplementation and Cardiovascular Risk in HIV

Principal Investigator: Grace McComsey, M.D.

Introduction/Purpose
You are being asked to take part in this research study because you are infected with Human Immunodeficiency Virus (HIV) and you are receiving HIV medications. People living with HIV have early signs of damage to their blood vessels. In this trial, the investigators are observing early indicators of vascular (blood vessel) damage that leads to heart disease seen in people with HIV. One such early indicator is zinc deficiency, which is thought to play a role in this damage. Fifty (50) subjects will be given zinc supplements on this study; 25 subjects will receive a dose of 45 mg and 25 subjects will receive a dose of 90 mg. The purpose of this study is to determine if zinc can reduce risks of heart disease. To qualify for this study, you must have a viral load of 400 copies/mL or less for the last 4 months and be taking your HIV medications for at least 12 weeks (and have taken HIV medications for a total of 6 months or more).

Before you decide whether or not to take part in this study, the study team would like to explain the purpose of the study, how it may help you, any risks to you, and what is expected of you.

Study Procedures
To be part of this study, you must be willing to:

1. Complete 5 study visits over 16 weeks
2. Have blood tests
3. Have height, weight, waist, and hip measurements taken
4. Have a brief physical examination
5. Have a DEXA (x-ray) scan
6. Have a REE (resting Energy Expenditure)
7. Have a test to see if your heart vessels are calcified
8. Have an Endopat procedure
9. Answer questions about your health and your smoking habits
10. Take daily zinc supplements that we provide
11. Take your HIV medication while in the study (unless your doctor does not think you should)

Screening

Before you enter, you will be asked to visit the clinic at least once to be screened and ensure that you meet the requirements for entry into the study. Screening may take place on the same day as a normally scheduled clinic appointment, as long as you are fasting. Before any tests can be obtained as part of this study, you would have to decide whether or not you would like to participate in this study. If you choose to enroll, this informed consent form will be signed. A targeted physical examination will be performed and recent blood work will be reviewed to be sure that you meet the inclusion criteria. The HIV-1 RNA, and HIV testing to confirm HIV status will be obtained from the clinical chart as these are a part of routine care. For woman of reproductive potential, a

urine sample will be taken for pregnancy test. Some of the plasma and serum will be stored for potential future testing such as additional tests for inflammation, cardiovascular markers, endothelial function markers, oxidative markers. These blood samples will be batched and the tests will be done at the end of the study and are part of this study.

Study Entry/On-study evaluations

For the first study visit (the entry visit into the study), you will be asked to "fast." That is, you will be asked ***not to eat or drink anything*** except your HIV medications and the usual amounts of plain water for at least 8-hours before you come in for this visit. If you must take medication with food, you will be asked to bring your medicines with you to the study visit so that you can take them with food after your blood has been drawn and tests has been completed. This visit must be within 30 days of your screening visit. The following procedures will be done at the first visit.

- At this visit you will have a medical history and a targeted physical exam done. You will also be provided with questionnaires to assess your diet, level of physical activity, alcohol and smoking intake.
- You will then have approximately 8 tablespoons of blood taken from a vein in your arm for laboratory tests. These tests include: tests to measure the amount of blood vessel damage that is present, tests to measure the amount of inflammation in your body, tests to check your blood sugar and insulin levels (insulin is the hormone that controls blood sugar levels in the body), a test for lipids like cholesterol, a complete blood count to check the number of white and red blood cells as well as platelets (the cells that help blood clot), a test to check your electrolytes (salts in your body) and tests for your kidney and liver function. A HIV viral load and CD4 count will be obtained from your clinical chart as these will be done as part of routine care.
- You will have a special X-Ray called DEXA scan that will measure the amount of fat in your entire body. DEXA uses a whole body scanner that rapidly directs x-ray energy from two different sources in an alternating way. This allows to read bone density and soft tissue mass simultaneously. During the DEXA scan, you will be lying down on the examining table and will have to be still for the duration of the test which is usually 10-20 minutes. Results will not be available until the end of study.
- You will have a test to measure REE (resting energy expenditure). You will be required to rest for about 20 min. Then a face mask with a nose clip will be placed for about 10 minutes. You will have to breathe by mouth into a device during this time. The nose clip and mask can be slightly uncomfortable for some people. Each session will take about 20-30 minutes.
- A CT scan of your heart (without contrast) will give a scoring for the calcium found (if any) in your coronary arteries. The scan will also measure the amount of fat deposits around the heart. This test takes about 15-25 minutes.

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- EndoPAT will be performed at this visit. This is a painless test that involves a finger probe to measure blood flow. A blood pressure cuff will be applied to your upper arm and inflated for approximately 5 minutes. After release of the cuff, the machine will measure the return of normal blood flow. This test will take about 30 minutes to do. Results will not be available until the end of study.
- You will be given a zinc supplement capsule to be taken every day while on study. You will be randomly given a dose of 45 mg (one capsule), or 90 mg (two 45 mg capsules), which you will take once per day with food. If you lose or misplace the capsules at any time, please call us to receive replacements at **216-844-2739**.
- You will be asked to give urine and stool specimens which will be stored for possible future testing for substances that could indicate organ damage. Some of your blood will be stored for future testing such as additional tests for blood vessel damage, tests that indicate risk of heart disease, additional tests for bone metabolism, inflammation, and additional testing of oxidative markers (markers of levels of free radicals in your blood). Free radicals are waste substances produced by our body that can damage tissues, like the heart vessels. These blood samples will be batched and the tests will be done at the end of the study. In addition, some of this stored blood may be used for measurements of antiretroviral concentrations. Results will not be available until the end of study.
- Your total duration of the study visit will be approximately 1 hour.

The follow-up study visits at the clinic visits will be at 4, 10 and 16 weeks (end of study). You will need to ***come fasting*** for all visits. ***No food or drinks for 8-hours*** before these visits. At each of these visits, patients will be asked about symptoms or any change in health status. A short targeted physical exam will be done.

- You will bring your zinc capsules to all visits. We will count them and return them or order more capsules as needed.
- At all visits, a HIV viral load and CD4 count will be obtained from your clinical chart as these will be done as part of routine care.
- Blood will be collected at all visits; approximately 4 tablespoons at week 4 and 10
- Also at week 16, additional testing will be done (similar to baseline visit) to check for inflammation markers, oxidative markers, glucose and insulin. Lipids, HIV-1 RNA, and CD4 count will be obtained from the clinical chart. Also a urine pregnancy test will be done if applicable. In addition, for study week 4, 10 and 16, some of the blood will be stored for potential future testing such as additional tests for inflammation, oxidative stress, immunology, and cardiovascular and metabolic markers. Patients will also be asked about diet and level of physical activity.

Premature study discontinuation

If you withdraw from the study before week 16, you will be asked to come back for final study evaluations. The evaluations to be performed at this premature study visit will be the same as the evaluations outlined for week 16.

Risks

The risks for taking part in this study are:

Blood Draw

Risks associated with drawing blood include: pain, bleeding, and bruising at the site of the blood draw. Other rare risks include: lightheadedness and/or fainting or infection at the site.

Zinc Supplementation

At the dose used, uncommon side effects include nausea, vomiting, abdominal pain (gastritis). At higher doses and when used for a long periods (years), copper deficiency and related anemia may happen. This is an extremely unlikely since we are only given 45 mg, or 90 mg, daily and for up to 16 weeks. Such doses have been shown to be safe even when given for 12 months to elderly frail subjects. In addition, in diseases such as Wilson's disease, zinc is given at a dose of 50 mg three times daily for prolonged durations. We will closely monitor your blood draws for chemistries, hematology and liver enzymes every 6 weeks, and as needed between study visits.

Fasting

Some individuals find fasting to be bothersome. It may make some individuals feel anxious, irritable, or hungry. Patients who are required to take their morning medications with food should wait until after the visit has been completed to take their medications. In addition, there may be other risks or side effects that cannot be anticipated at the present time. You will be carefully monitored during the entire study.

Pregnancy

Zinc may not be safe for unborn babies. Women must have a pregnancy test before they enter this study. The pregnancy test must be negative. In addition, **if you think you may be pregnant** at any time during the study, you are to tell the study staff right away. In the event that you become pregnant while on study, you will be taken off study, and no further evaluations or tests will be performed as part of the study. If you are of reproductive potential, you must agree to use at least 2 forms of birth control until 6 weeks after the study ends.

Radiation associated with DXA scan and CT

We have included one whole body DEXA scan in order to measure adipose in each subject. There is a risk with DEXA and CT scans, which is related to the accompanying radiation exposure. However, the risk is minimal as the radiation exposure is small, about 1/10 the dose of a standard chest x-ray, or about 3% of the total radiation that the average person living in the United States

receives from the environment in a day. Radiation to a human embryo may also cause birth defects. Negative urine pregnancy tests will be documented within 4 days of the DEXA and CT scan that is performed in a female of child-bearing potential. The DEXA scan will take approximately 20 minutes total to complete, and subjects will have to lie still during the procedure, but it is non-invasive and does not cause any pain. The CT will take approximately 15 minutes total to complete and is non-invasive.

EndoPAT. This is a painless imaging tests and have no short or long-term risks. The EndoPAT test may be mildly to moderately uncomfortable because of the blood pressure cuff that is applied tightly to your arm.

Other risks
You should tell your study doctor or study nurse about all other drugs you are currently taking including non-prescription medications, alcohol, recreational, and herbal products. In addition to the risks and discomforts listed here, there may be others that are currently not known.

Benefits

There may be no direct benefit to patients from participating in this study. Your participation in the study will allow collection of valuable information about the effect of HIV infection on cardiovascular disease. This information may be useful to you and other people with HIV disease.

Alternatives to Study Participation

Alternatives to your participation in this study are not to participate and to receive the standard of care from your primary care doctor.

Financial Information

Cost to participants
There is no cost to participants for the study related clinic visits, examinations or laboratory test required by this study. Medical costs of other treatment or examinations outside of the study will be the responsibility of the patient or their insurance company. If during the study, subjects suffer from symptoms requiring any of the tests done within the study evaluations (but outside of the study window period), they will have these tests ordered by their primary care provided and charged to the subject insurance.

Compensation
For completed study visits screening, week 4 and week 10, patients will receive $25.00 that day. Entry and week 16, patients will receive $50.00 that day (total of $175 for completing the entire study). This payment will help cover the expense of childcare, transportation and time off work

that patients may incur as a result of being in this study. To help with the cost of gas, for participants traveling > 20-40 miles one way for their appointments, they will also be given a $15.00 gas card to cover the cost of the transportation. Participants traveling > 40 miles one way for their appointments will also be given a $30.00 gas card to cover the cost of transportation. . Subjects will be asked to fast (nothing to eat or drink for 8 hours prior to visit) at entry, week 4, week 10 and week 16, therefore a $5.00 meal voucher will be provided for subjects to use in the University Hospitals cafeteria. In addition either one all day RTA pass will be provided or a parking voucher to use in designated University Hospitals parking garages will be provided to cover the cost of transportation.

Other information

If your blood sample is lost, broken, or if there is not enough blood taken at the original visit, your sample will not be able to be tested and you will be asked to return to the clinic for another blood sample. You will not receive additional compensation for this visit or blood sample. The chance of being asked to return to the clinic for another blood sample is small.

If the study is changed in any way or if new information is learned that could affect your participation, you will be told about the changes and information. Also, you may be asked to sign a new consent form.

U.S. NATIONAL INSTITUTES OF HEALTH (NIH) CLINICAL TRIAL DATABASE: A description of this clinical trial will be available on http:///www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time to find out information about the trial and basic results.

Confidentiality

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally. All laboratory specimens, evaluation forms, reports, and other study materials will be identified by a coded number to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done with coded numbers only.

Student/Employee Rights

Choosing not to participate or withdrawing from this study will not affect your employment or class standing, nor the will results be shared with your supervisor.

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What happens if I am injured?

If injury occurs as a result of your involvement in this research, medical treatment is available from University Hospitals Case Medical Center or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Involuntary Withdrawal from the Study

Your study doctor has the right to stop the study at any time, with or without your consent, for any of the following reasons:

- The study is cancelled by the site's institutional review board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.), the sponsor or the Food and Drug Administration (FDA).
- If you have a bad effect from the study procedures
- If your doctor decides it is in your best interest
- If you become pregnant
- If you become incarcerated
- If you do not come to 2 visits in a row

Privacy of Protected Health Information

The Health Insurance Portability & Accountability Act (HIPAA) is a Federal law that helps to protect the privacy of your health information and to whom this information may be shared within and outside of University Hospitals. This Authorization form is specifically for a research study entitled "*Pilot Study of Zinc Supplementation and Cardiovascular Risk in HIV*" and will tell you what health information (called Protected Health Information or PHI) will be collected for this research study, who will see your PHI and in what ways they can use the information. In order for the Principal Investigator, Dr. Grace McComsey, and the research study staff to collect and use your PHI, you must sign this authorization form. You will receive a copy of this signed Authorization for your records. If you do not sign this form, you may not join this study. Your decision to allow the use and disclosure of your PHI is voluntary and will have no impact on your treatment at University Hospitals. By signing this form, you are allowing the researchers for this study to use and disclose your PHI in the manner described below.

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Generally the Principal Investigator and study staff at University Hospitals and Case Western Reserve University who are working on this research project will know that you are in a research study and will see and use your PHI. The researchers working on this study will collect the following PHI about you: your demographic information, such as your age, ethnicity and body mass index (BMI); your medical history, including information about medical conditions that may affect your treatment, including conditions related to mental and behavioral health, psychiatric disorders, and alcohol and drug dependence or abuse, specific information about your antiretroviral therapy and any other medications you are taking just before and during the research study, numbers or codes that identify you, such as your social security number, medical record number, and research study case number. This PHI will be used to evaluate the safety of smoking cessation in decreasing blood vessel damage and inflammation, as well as lipids, blood sugar and the body's sensitivity to insulin. Your access to your PHI may be limited during the study to protect the study results.

Your PHI may also be shared with the following groups/persons associated with this research study or involved in the review of research: study nurses; staff of the Smoking Cessation Program; other staff from the Principal Investigator's medical practice group; University Hospitals, including the Center for Clinical Research and the Law Department; Government representatives or Federal agencies, when required by law.

Your permission to use and disclose your PHI does not expire. However, you have the right to change your mind at any time and revoke your authorization. If you revoke your authorization, the researchers will continue to use the information that they previously collected, but they will not collect any additional information. Also, if you revoke your authorization you may no longer be able to participate in the research study. To revoke your permission, you must do so in writing by sending a letter to Grace McComsey, M.D. at Rainbow Babies and Children's Hospital, Pediatric Infectious Diseases, 11100 Euclid Ave, Mailstop RBC 6008, Cleveland, OH, 44106. If you have a complaint or concerns about the privacy of your health information, you may also write to the UH Privacy Officer, Management Service Center, 3605 Warrensville Center, MSC 9105, Shaker Heights, OH 44122 or to the Federal Department of Health and Human Services (DHHS) at DHHS Regional Manager, Office of Civil Rights, US Department of Health and Human Services Government Center, JF Kennedy Federal Building, Room 1875, Boston, MA 02203. Complaints should be sent within 180 days of finding out about the problem.

The researchers and staff agree to protect your health information by using and disclosing it only as permitted by you in this Authorization and as directed by state and Federal law. University Hospitals is committed to protecting your confidentiality. Please understand that once your PHI has been disclosed to anyone outside of University Hospitals, there is a risk that your PHI may no longer be protected; however other Federal and State laws may provide continued protection of your information.

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Summary of your rights as a participant in a research study

Your participation in this research study is voluntary. Refusing to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Case Medical Center (UHCMC) or elsewhere; however, UHCMC has no plans to provide free care or compensation for lost wages.

Disclosure of your study records

Efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Case Medical Center Institutional Review Board may review your study records. In addition, for treatment studies, the study sponsor and possibly foreign regulatory agencies may also review your records. If your records are reviewed your identity could become known.

Data sharing

At times, other investigators who are not involved with this project may request access to the data collected from you and other participants in this study. This is sometimes done so that data may be reviewed and analyzed in ways that are different from the original study. With your permission, we would like to share your de-identified data (**no name or personal information will be shared**) with other investigators, should such a request be made. Please check either YES or NO in the boxes below:

☐ Yes, I allow my data to be shared ☐ No, do not share my data

Contact information

_____ has described to you what is going to be done, the risks, hazards, and benefits involved. The Principal Investigator, Dr. Grace McComsey, can also be contacted at **216-844-2739**. If you have any questions, concerns or complaints about the study in the future, you may also contact them later. If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about; concerns regarding the study; research participant's rights; research- related injury; or other human subject issues, please call the University Hospitals Case Medical Center's Research Subject Rights phone line at (216) 983-4979

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or write to: The Chief Medical Officer, The Center for Clinical Research, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakeside 1400, Cleveland, Ohio, 44106-7061.

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

X	
Signature of Participant	Date
X	
Printed Name of Participant	

X	
Signature of person obtaining informed consent	Date
X	
Printed name of person obtaining informed consent	

X	
Signature of Witness	Date
X	
Printed Name of Witness	