Vanderbilt University Institutional Review Board
Informed Consent Document for Research

Principal Investigator: T. Alp Ikizler, MD **Revision Date: 06/02/2015**
Study Title: Nutrition, Inflammation and Insulin Resistance in End Stage Renal Disease—Aim 2
Institution/Hospital: Vanderbilt University Medical Center

This informed consent applies to adult hemodialysis patients aged 21 and older.

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study. Anyone you authorize to receive your medical record will also get this note.

1. What is the purpose of this study?

You are being asked to take part in this research study because you have kidney disease and you are on chronic hemodialysis. Most hemodialysis patients have poor nutritional status. Certain things related to your kidney disease could be making your nutritional status worse. The purpose of this study is to examine the effects of two of these things. These are inflammation (how your body reacts to an injury) and insulin resistance (how your body uses sugar).

2. What will happen and how long will you be in the study?

We plan to enroll about 45 people like you who are on chronic hemodialysis (CHD). All procedures are for research purposes. The study requires two separate overnight study visits at Vanderbilt's General Clinical Research Center (GCRC). At each visit, we will measure your metabolism (how your body uses protein and calories). We will also examine your insulin resistance. In between the two overnight visits (about 6 weeks into the study), you will also need to come to the GCRC for a short visit. You will be in the study about 4 months.

Screening Visit (about 2 weeks before the first overnight study visit)

We will have one visit to tell you about the study, have you sign the consent form if you wish to participate, and ask you demographic questions such as age and race. We will also talk to you about the medications you take.

If you have not had a tuberculosis (TB) skin test within the last 3 months, we will place this in your forearm. We will need to read the skin test within 48-72 hours. This is to confirm you do not have TB.

If you have not had an HIV, Hepatitis C or Hepatitis B test within the last month, we will also test you for this. If so, we will draw a teaspoon of blood. This is to confirm you do not have HIV, Hepatitis C or Hepatitis B.

HIV (human immunodeficiency virus) is the virus that causes the acquired immunodeficiency syndrome (AIDS). This blood test is required to enable us to exclude study participation of HIV-positive individuals. Your Primary Care Provider will be provided with the results of the testing (positive or negative). Vanderbilt is required to report positive results to the Tennessee State Board of Health. If your test is positive, your Primary Care Provider will tell you the results and provide counseling and any indicated follow up medical care. The follow up care is not part of this research study and upon a positive result we will withdraw you from the study for your safety. The test results will be kept fully confidential to the extent permissible under the law. If you do not want to be tested for HIV, then you should not agree to participate in this study.

If your test results for TB, Hepatitis B, or Hepatitis C are positive, it will be reported to the Tennessee Department of Health and you will be given a referral for appropriate medical care.

General Overview of the Study

Two weeks before each overnight study visit you will be asked to eat a set amount of protein and calories. During these two weeks, you will be called 2 times. You will be asked to tell us what you have had to eat. Each call will last about 15 minutes.

Within 2 weeks of each of the three study visits we will measure how much fat and muscle you have. This is called a DEXA scan. If you are a female of child-bearing potential we will draw about a teaspoon of blood to check for pregnancy before the DEXA scan. You will also be asked to perform a simple hand grip test at each study visit.

After you complete the first metabolic clamp study, you will receive either a drug that blocks inflammation (Anakinra) or a placebo on 36 dialysis treatment days (12 weeks). A placebo is something that looks just like the drug however it does not contain any active medicine. The chance that you receive the drug or the placebo will be determined by something like the toss of a coin. The drug or placebo will be given to you on the days you have dialysis at your dialysis unit, so you do not have to travel extra. The drug or placebo will be given under your skin by injection. We do not want you to miss any treatments during these 12 weeks. If you do, the study doctor will decide whether or not you can continue in the study. The drug or placebo will be provided to you by the research team.

You will also receive either a drug that decreases insulin resistance (Actos) or a placebo every day for 12 weeks. You will take 1 pill per day by mouth. A placebo is something that looks just like the drug however it does not contain any active medicine. The chance that you receive the drug or the placebo will be determined by something like the toss of a coin. A bottle of drug or placebo will be given to you that has enough pills for 4 weeks. You will get 3 bottles of pills during the study. We do not want you to miss taking any pills during these 12 weeks. If you do, the study doctor will decide whether or not you can continue in the study. The drug or placebo will be provided to you by the research team.

By chance, you will receive either (a) Anakinra injection and placebo pill, (b) placebo injection and Actos pill, or (c) placebo injection and placebo pill.

We will check your blood count every week at dialysis. If you have had your blood count already checked as part of standard of care for the week we will record this. If you have not had your blood count checked we will do this for research purposes. We will draw about ½ teaspoon of blood at dialysis to check your count. This is a total of a little more than 1 tablespoon of blood over the 3-month study.

After you have completed about 6 weeks of drug or placebo, we will collect a little more than 1½ tablespoons of blood. You will be asked to come to the visit in a fasted state. This means you cannot eat anything for 6 hours before the visit. You will also have a DEXA scan and perform a hand grip test.

After you have completed the 12 weeks of drug or placebo you will repeat the metabolic clamp study. We will contact you throughout the next 2 weeks for follow-up and post study blood draw. This blood draw will be about ½ teaspoon to check your blood count.

Metabolic Clamp Study:

The two metabolic clamp studies will happen at the GCRC. Each study will be scheduled on a non-dialysis day. You will come to the GCRC the night before each study and spend one night. We will provide you dinner and a snack with set amount of protein and calories. After about 8 PM you will be fasting. You will only be allowed to drink water after that.

The next morning, you will be asked one time to breathe into a "metabolic cart" for about 10-20 minutes. We will also measure the rate at which blood flows through your arm or leg. Afterwards, dialysis needles will be placed in your shunt. Blood will be drawn to collect baseline data. We will also collect a sample of your breath. An IV will be started with a solution that has combination of glucose and amino acid solution. We call this a 'tracer'. Amino acids are the building blocks of proteins. Your dialysis access will be used to do this procedure. The infusion will continue through the whole study. A venous catheter (IV) will be placed in the arm without your access. The catheter IV will be used to draw blood at specific time points.

During the first two hours of the study, we will measure again the rate at which blood flows through your arm or leg.

Two hours after starting the tracer, we will have a 'sampling period'. During the sampling period we will draw blood every 5 minutes for 30 minutes. Also during this time, you will be asked two times to breathe into a bag for several breath cycles.

After the 'sampling period', insulin supplementation will be started at a set rate. The amino acid supplementation may be started at the same time or may be delayed. During this time small amounts of blood will be drawn every 5 minutes. This is to check your blood glucose levels. Every 10 minutes we will check the amino acid levels. The infusion will run for about 1-3 hours. After the insulin begins, your glucose level will be adjusted to a normal range. This will be maintained at that level by providing you a glucose infusion as needed.

After 90-180 minutes (depending on how quickly your blood sugars stabilize), we will sample your blood for 30 minutes. Again, during this time you will be asked two times to breathe into a bag for several breath cycles. We may collect another set of samples if the amino acid infusion was delayed. Potassium levels will be checked every 30 minutes to monitor any changes. If your potassium is low, we will give you potassium through your vein.

If you urinate during the study, we will collect a sample of your urine. After the study is completed, all infusions except for glucose will be discontinued. The glucose solution will be gradually decreased over time. Your blood glucose will be checked every 15 minutes. Once your blood glucose level is stable, the glucose solution will be discontinued. We will continue to monitor your blood sugar every 15 minutes for about an hour. The IV catheter and your dialysis access needles will be removed. You will be allowed to eat after the study. We may perform a short post-study dialysis treatment at the GCRC or at one of the outpatient dialysis clinics. This will depend on your clinical status (labs and fluid intake). This will be determined by a doctor or a nurse practitioner. This dialysis treatment is not for research. This treatment will not take place of your normal dialysis treatment. You will receive standard discharge instructions including contact information before leaving the GCRC. We will follow up with you within about 1 week of the study visit.

Description of Procedures During the 2-day Metabolic Clamp Study (Performed for Research Purposes)

DEXA Scan

We will measure how much fat and muscle you have. This will be done within 2 weeks of each metabolic clamp study, as well as the visit at week 6. We will do this by a test called dual energy x-ray absorptiometry (DEXA). For the DEXA, you will lie on a bed for 15-20 minutes while a scanner X-rays your body fat, lean muscle, and bone masses. If you are a female of childbearing potential, we will do a pregnancy test before the DEXA to make sure you are not pregnant.

Heart Monitoring

We will monitor your heart rhythm and rate during the clamp study. This will be done by placing sticky pads (electrodes) on your chest. The sticky pads are connected to wires (leads) that hook up to a machine. This way we can monitor your heartbeat and heart rhythm.

Blood Draws

In total, a little less than a cup of blood will be obtained during each overnight study visit.

Women of child-bearing potential will have about a teaspoon of blood drawn before the overnight study visits. This is to confirm non-pregnancy status prior to each clamp study.

Breath Samples

You will be asked to breathe into a breath collection bag at specific times during the clamp study. We will collect the air you breathe out.

Metabolic Cart

One time before the clamp study begins you will be asked to breathe into a "metabolic cart" for about 10-20 minutes. This machine measures the oxygen and carbon dioxide content of your breath. This lets us know how much energy you use. This machine may use a mouthpiece and a nose clip to help channel your breath to the machine.

Arm/leg Blood Flow

We will measure the rate at which blood flows through your arm or leg two times. Once before the clamp study begins. The second during the first two hours of the clamp study. This involves placing three blood pressure cuffs on your arm or leg without your access. The cuffs send an electronic signal to a computer that estimates the rate at which blood flows through your arm or leg.

Description of Procedures and Timeline of Study

Weeks -2 to 0.	Week 0.	Weeks 0 to 12.	Week 6.	Weeks 10 to 12.	Week 12.	Week 13-14.
Continue regular treatment at dialysis unit.						
Possible blood draw at dialysis, 2 weeks of recommended diet, 2 random diet recalls, and DEXA & hand grip test at GCRC	Overnight stay at the GCRC and metabolic clamp study.	Study drug administration • 3 injections per week • 1 pill per day	Blood draw at dialysis and DEXA & hand grip test at GCRC	2 weeks of recommended diet, 2 random diet recalls, and DEXA & hand grip test at GCRC	Overnight stay at the GCRC and metabolic clamp study.	Follow up blood draw at dialysis

OPTIONAL PROCEDURE:

Muscle Biopsy: The muscle biopsy is for research purposes only. If you have a dialysis shunt in your thigh you will not be able to complete this procedure. The biopsy will give us more information on how your body handles nutrients. Before and after the metabolic clamp study, a muscle biopsy will be taken from the mid-thigh area. The first biopsy will use one thigh muscle and the second biopsy will use the other thigh muscle. Lidocaine will be used to numb the area where the biopsy will be done. A small incision (about an inch) will be made in the skin. A special needle will be used to withdraw the muscle tissue. The amount will be about the size of a pencil eraser. Any bleeding will be stopped with a pressure dressing.

Do you consent to the Muscle Biopsy part of the study? (Please place your initials in the space in front of your response.):

____ Yes. ____ No.

3. Costs to you if you take part in this study:

If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research.

However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

4. Side effects and risks that you can expect if you take part in this study:

1. Inconvenience of reporting to the GCRC and staying one night for each metabolic clamp study.
2. The insulin infusion during the clamp study can lower blood potassium levels. If this drops too low, your heart rhythm may be affected. We will closely monitor potassium levels (every 30 minutes), and place you on a machine that monitors your heart to decrease this risk and observe any complications. If a decrease in potassium occurs, it will be replaced immediately intravenously.
3. Replacing the potassium may cause slight burning or irritation and your heart rhythm may be affected. We will monitor your heart to decrease this risk. We may adjust the rate of replacement as needed.
4. There is a small risk of low blood sugar during the clamp study. If this occurs, you may experience any of these symptoms: feeling lightheaded, headache, fast heartbeat, sweating, blurred vision, hunger, and rarely seizures. We will check blood sugar every 5 minutes. If the blood sugar level drops below normal, it will be restored intravenously.
5. Inconvenience of having sticky pads placed on the chest and being connected to a heart monitor during the clamp study. The sticky pads used for the ECG monitoring may cause skin irritation.
6. Having to lie still for 10-15 minutes during the DEXA scan may be uncomfortable.
7. The DEXA scan uses x-rays (or radioactivity). You will be exposed to a small amount of radiation. The radiation exposure that you would likely receive from a total of three DEXA scans is approximately equal to one month of exposure from natural background sources. If you are a female of childbearing potential, we will do a pregnancy test before the DEXA to make sure you are not pregnant.
8. The IV placed in your forearm may cause a slight bruise and carries a risk of infection which is rare.
9. Eating a recommended diet for 2 weeks and providing 2 food recalls may be inconvenient.
10. Breathing through a mouthpiece may be inconvenient for you and may make you feel lightheaded or dizzy.
11. The blood pressure cuffs placed on your forearm/leg may be uncomfortable when inflated. For each blood flow test, one cuff will remain inflated up to 2 minutes. Another cuff will be inflated/deflated about 9 times over 2 minutes. The third cuff will remain uninflated.
12. Inhaling and exhaling into the breath sample bag may be an inconvenience, but it does not pose any risk.
13. The isotopes used in the metabolic studies are not radioactive and do not present any additional risk.

14. The fistula needles placed in your arm or leg carry a risk of infection. This is rare. Your access will be cleaned before inserting the needles.
15. The lidocaine used for local anesthetic prior to IV insertion or prior to muscle biopsy. This may cause numbness, burning and/or local rash or irritation, if you are allergic. There is a risk that lidocaine may cause problems with heart rhythm. This is unlikely given the amount you will receive.
16. You will be asked not to take birth control pills during the study due to possible drug interactions.
17. You should avoid getting flu shots or other vaccines during the study period.
18. The pills used in this study (Actos) can cause or make congestive heart failure worse in some patients. There have been reports of liver toxicity, water retention and bone fractures. You will be monitored closely for signs of any of these adverse events. You may be withdrawn from the study if you experience any of these events.
19. The injection used in this study (Anakinra) has some adverse effects such headache and redness/pain at the injection site. If these effects persist or worsen, notify the study doctor promptly. Other less common side effects include nausea, diarrhea, abdominal pain, sinus problems, and/or flu-like symptoms. If these effects occur, contact the study team immediately. This drug may rarely cause a decrease in your white blood cell (WBC) count, which could be life threatening. We will monitor your WBC count on a weekly basis to make sure your WBC is within normal limits.
20. Risk of injected placebo includes redness/pain at the injection site.
21. The PPD tuberculosis skin test may cause mild pain at the injection site.
22. Taking the placebo pills may be an inconvenience.
23. The optional muscle biopsy may cause muscle soreness, bruising, or infection. It may also result in a small blood-filled bump at the biopsy site. There is a small chance that some slight bleeding may also occur. The soreness may last as long as 48 hours.

5. Risks that are not known:

Because this study is being done for research only, there may be risks that we do not know about at this time. If new risks become known, you will be informed of these risks.

If you are a woman and are able to become pregnant, you will have a blood test to make sure that you are not pregnant before you receive treatment in this study

6. Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

7. Good effects that might result from this study:

a) The benefits to science and humankind that <u>might</u> result from this study are an increased understanding of the effects of insulin resistance and inflammation sensitivity on protein energy wasting in hemodialysis patients.

b) The potential benefits you might get from being in this study: You will receive no direct benefits from participating in this study.

8. Other treatments you could get if you decide not to be in this study:

Taking part in this study is voluntary. You may choose not to take part in the study. If you choose not to take part in the study, your doctor will explain other options.

9. Payments for your time spent taking part in this study or expenses:

We will ask you for your Social Security number and address before you are compensated for taking part in this study.

We will compensate you $200 for each metabolic clamp study (maximum of $400) and $20 for the visit at week 6. We will also compensate you $10 for each week you take study drug (maximum of $120). If you choose to participate in the optional muscle biopsy you will be compensated $100 for each biopsy (maximum of $400). The total amount that you will be compensated to complete both metabolic clamp studies and the visit at week 6, take study drug for 12 weeks, and all four optional biopsies is $940. If you drive, you will be reimbursed for mileage.

This amount may be taxable and will be reported to the Internal Revenue Service (IRS).

10. Reasons why the study doctor may take you out of this study:

If you are unable to complete study procedures or if you do not follow the study plan, you may be taken out of the study. If you are removed from the study you will be told the reason.

11. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact the Principle Investigator, **Dr. Alp Ikizler,** at **615-343-6104.** You may also call the Nephrology answering service at **615-343-7592**.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Clinical Trials Registry.

A description of this clinical trial will be available on 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 the results. You can search this Web site at any time.

14. Confidentiality:

All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. Each participant will be assigned a study number and will be referred to by this number to protect their identity over the course of the study. Data will be stored on a password protected computer. Paper case report forms and other pertinent paper documentation will be kept in a locked office and only study personnel will have access.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Ikizler and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

15. Authorization to Use/Disclose Protected Health Information

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Ikizler and his study team may share the results of your study and/or non-study linked laboratory tests, as well as parts of your medical record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections and the Vanderbilt University Institutional Review Board, and VATVHS Nashville. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Ikizler in writing and let him know that you withdraw your consent. His mailing address is 1161 21st Ave. South, S3223 MCN, Nashville, TN 37232. At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date	Signature of patient/volunteer

Consent obtained by:

Date	Signature
	Printed Name and Title