

DESCRIPTION OF STUDY

Principal Investigator: George A. Kaysen, MD, PhD
Title of the Study: CCRC: "The independent effects of level of kidney function and body composition on establishing HDL cholesterol levels" (220939-7)

PURPOSE AND PROCEDURES:

1. Describe the study format and whether it is single or multi-center; industry-sponsored or investigator initiated; and the funding source.

This is a single center cross sectional analysis of body composition and lipoprotein level and structure among patients with graded levels of renal failure in comparison to control subjects. This is not a treatment or outcome trial.

2. Briefly describe the specific aims of the study, research methods and procedures.

To establish the relationship between HDL cholesterol and both body composition and insulin resistance measured as HOMA among a cohort of non diabetic non proteinuric patients with advanced CKD, (stage IIIb, Stage IV and stage V) compared to non diabetic subjects having normal kidney function (eGFR \geq 80 ml/min)

3. Address if therapeutically removed tissue will be collected, what types, and for what purposes.

N/A

4. Specify the nature, frequency and duration of tests, if any.

There is a potential for blood to be drawn two times. In patients who are under immediate care with recorded fasting blood sugar values in the non diabetic range (less than 120 mg/dL) obtained in the past 6 months, no blood samples will be obtained for screening and patients will be studied or excluded based upon laboratory values in either the UC Davis or DCI. The creatinine available in the medical record will also be used to establish the level of renal function. In patients in whom no recent evidence is available to exclude diabetes and for the valuation of baseline renal function, approximately 5 cc of blood will be obtained to measure a fasting blood sugar and serum creatinine. Patients with fasting blood sugar values equal to or greater than 120 mg/dL will be excluded. Dialysis patients have blood drawn at least monthly making only a single sample necessary for these patients. Subjects who are not on dialysis, i.e. normal control subjects and patients having chronic kidney disease may require two blood samples - one 5 ml sample (1 teaspoon) and one 45 ml (3 tablespoon) sample obtained.

5. If blood samples will be collected, identify in what manner and the maximum amount that will be collected over any 6 week period (if subjects are co-enrolled in other research studies, the volume of blood from the other study should also be included):

venipuncture venous catheter arterial puncture arterial catheter cutaneous

6. Any additional procedures (noninvasive) involved in this study activity must be described.

Mass, lean tissue mass, and bone mineral content, using a Hologic Discovery W bone densitometer (Hologic, Bedford, Massachusetts) in accordance with standardized procedures recommended by the manufacturer. DXA measurements will be performed with the patient in the supine position, dressed in light clothing, and wearing no metal objects. Total body scanning time will be approximately 11 min, and the total x-ray radiation received by each patient will be approximately 0.4 mrem.

Whole body bioimpedance spectroscopy (BIS) measurements will be performed using two different devices: 1.) an ImpediMed (ImpediMed Limited., San Diego, CA); 2) the Xitron in all patients while patients are in the supine position at the CCRC. Dialysis patients will be studied on a non dialysis day. The areas for electrode attachment will be cleaned with alcohol. Two injecting electrodes for applying alternating current will be placed on

the ipsilateral dorsal surfaces of the hand (11) and the foot (12), and two sensing electrodes will be placed on the wrist and the ankle. Current is injected for a spectrum of 50 frequencies ranging from 5 kHz to 1 MHz. A computer is used for data acquisition, data storage, and data analysis. Extracellular resistance will be determined as the limit of resistance at zero frequency by fitting the impedance data using the modified Cole-Cole model with software supplied with the impedance device. The rationale for two BIS devices is the Xitron was used to develop our equations for body composition and we want to make certain the results of the two instruments are not significantly different in both the control and dialysis patient populations. Our standards are all with the Xitron, so we need to verify that we are getting the same results. Xitrons are no longer produced and are unavailable for purchase. We want to verify the equations we generated relating body composition performed with the Xitron work for the Impedimed. The Xitron is more difficult to use since the computer and measurement instrument are separate devices. The Impedimed is easier to use and portable. but for the patient they are identical.

Blood will be drawn at the CCRC at the same visit in which DEXA and BIS measurements are made to avoid multiple trips to the CCRC. The exception is for dialysis patients. In their case, to avoid unnecessary venipuncture, blood will be drawn immediately prior to a mid-week dialysis session. Heparin dose of 50U/kg will be given to these patients. For dialysis on this day, no heparin maintenance will be given thus eliminating additional risk.

Those subjects not receiving dialysis will receive an injection of heparin (50 U/kg) during the course of having blood drawn and are thus subjected to a small risk of increased bleeding for the 4-6 hour period following the injection. No additional venipuncture will be performed to administer the heparin.

7. If the study involves incomplete disclosure, provide the rationale.

N/A

8. If this activity will be utilizing existing data, specify the source and how the data will be retrieved, reviewed, coded and stored.

Urine Protein, Creatinine, medical history. In order to recruit subject with chronic kidney disease (CKD), initially ask or review medical record to check for inclusion criteria (no labs will be done at this time). If eligible then he/she will be enrolled. This permission will be obtained by consent.

9. Address the location and duration of the study including follow-up period.

The study will take about an hour and will be conducted at the CCRC located in the Cypress Building, 2221 Stockton Blvd. Suite D, Sacramento, Ca 95817.

10. Clarify how you plan to monitor data to ensure subject safety.

Labs with critical values are reported to Dr. Kaysen directly.

11. Address whether you have the appropriate resources (study personnel and facilities) to conduct this study.

We have requested funding for a half time clinical coordinator who will be dedicated to this study for 2 years. The PI and the co PI will each devote 5% effort to recruitment, safety monitoring and data analysis.

12. Describe the role of each key member of your study personnel.

- George Kaysen, MD --Physician/PI: write/collaborate on manuscript from data collected and oversees study
- Physician/Co-PI: consent/collaborate on manuscript from data collected and oversees study
- CRC/Lab Tech: enroll, consent, collect specimen(s) as well as run assays on specimen(s).

SUBJECT SELECTION:

1. Identify the subject population.

The study population will consist of 20 prevalent hemodialysis patients, 20 patients having an estimated glomerular filtration rate (eGFR) between 15 and 29 and 20 patients having an eGFR between 30 and 45. Thirty subjects having normal renal function (eGFR \geq 80 ml/min) will be studied. Patients must be non diabetic (FBS \leq 120 mg/dl, not taking oral contraceptives or hormone replacement therapy, not on steroids, not on HIV treatment regimen, not have a functioning renal transplant and not taking a lipid lowering agent at the time of the research study.

2. Address how subjects will be recruited: direct person to person solicitation, by telephone, letter, advertisement, press release, notices, other. Provide the text.

See attached recruitment flyer(s).

3. State from where subjects will be recruited, when and how many.

Patients will be recruited from the UC Davis chronic kidney disease clinics (Stage IIIb and Stage IV CKD, from the dialysis patient population at our 4 DCI dialysis clinics (University, Southgate, Madison, and Rancho Cordova, and if necessary from the DaVita dialysis units which we are affiliated. Normal subjects will be recruited through the and by posting notices at University of California Davis, and on the bulletin boards at the UC Davis main campus.

Will be recruiting from outside of UC Davis and DCI using IRB approved methods.

4. Specify the age of the research subjects.

18-75 years old.

5. List all criteria for including and excluding subjects.

Inclusion: Subjects will be recruited who are between 18 and 75.

Inclusion criteria:

- Men and women - ages 18-75
- Self report of stable body weight during the past six months
- BMI 18-40 kg/m²
- Hemodialysis dependent for at least 3 months (prevalent ESRD cohort)
- eGFR \geq 15 \leq 44 ml/min (CKD cohort)
- eGFR \geq 80 ml/min (Control cohort)

Exclusion Criteria:

- Diabetes Mellitus (American Diabetes Association definition: fasting glucose $>$ 120 mg/dl)
- Evidence of liver-hepatitis B, or thyroid disorders
- HIV by medical history (HIV test will not be performed)
- Renal transplant recipient
- Oral contraceptive, hormone replacement therapy
- Systemic use of systemic or inhaled corticosteroids in the past month
- Contraindication to systemic anticoagulation (heparin administration is necessary to measure levels of LPL, HL).
- Hemoglobin $<$ 8.5 g/dl (anemia)
- Current, within 2 months use of any hypolipidemic or anti-diabetic agents.
- Any other condition that, in the opinion of the investigators, would put the subject at risk
- Patients treated with a fibric acid derivative or niacin in the past 4 weeks.
- Urinary protein excretion of greater than 0.5 grams per day.

Patients will be screened by collection of serum for fasting blood sugar, creatinine, and measurement of urine

6. If women and minorities are excluded, provide rationale for such exclusion.

N/A

7. Attach the translated documents for subjects whose primary language is not English.

N/A

SPECIAL/VULNERABLE POPULATION (if applicable):

Surrogate consent for participation in a research study should be employed only to the extent that it is consistent with the intent of the Common Rule (45 CFR 46, Subpart A) and all other federal and state laws and regulations pertaining to protecting human subjects participating in research. Carefully review the IRB Policy on *Surrogate Consent For Research* for compliance with all applicable laws, regulations, and conditions of this policy. Investigators are reminded that use of surrogate consent shall apply on a case-by-case basis within the protocol.

1. Identify the vulnerable population: ___ children, ___ mentally handicapped, ___ pregnant women, ___ fetuses, ___ prisoners, ___ cognitive impairment, ___ life-threatening disease, or ___ social or ___ economically disadvantaged. Address what additional safeguards you will put into place to protect the rights and welfare of this population.

N/A

2. If you are seeking IRB approval for use of surrogate consent, justify the appropriateness of such use and describe your specific plan for the assessment of the decision-making capacity of the subject(s).

N/A

RISKS:

1. Address whether there is a possibility of physical, psychological, social or legal injury from participation in this study and assess the likelihood and seriousness of those risks.

Hyperlipidemia: During recruitment/screening, it may be determined that a potential subject qualifies for lipid therapy under NCEP guidelines. Subjects identified with existing hyperlipidemia will be informed of the small, but potential risk of delaying treatment during the study period. They will be informed they have the option to not participate in the study and begin the lipid-lowering therapy recommended by their physician.

Blood Collection: There is potential for bruises at the site blood collection procedures. The volume of blood collected during all procedures will be within guidelines for minimal risk blood draw.

There is a chance of bruising, or very rarely, an infection at the site where blood will be taken. Proper aseptic blood collection techniques will be used to minimize these risks.

Heparin: Patients will each receive a single dose of heparin. This imparts a small risk of hemorrhage.

Heparin will be administered to non dialysis patients while the patients are in the CCRC minimizing the risk of trauma during the period of systemic anticoagulation. There is a small risk of bleeding from Heparin.

Patients who are on dialysis receive heparin as a component of dialysis treatment. Blood will be drawn prior to dialysis initiation, but no additional needle stick or heparin administration will be required of these patients.

DEXA: Subjects will be exposed to a very small amount of x-ray radiation (0.4 mrem) for each DEXA procedure. There are no known health risks associated with radiation exposure levels this low.

2. If the methods of research create potential risks, describe other methods, if any, that were considered and why they will not be used.

The risks involved are minimal. It is not possible to measure the levels of the relevant enzymes without heparin administration. The exposure to ionizing radiation is approximately equal to that exposure received by dental X-rays. The outcome of interest is dyslipidemia. It is not possible to explore this in the at risk population without withholding lipid lowering drugs for approximately 60 days if the patients are already being treated.

3. Identify your plan for protecting subject privacy and confidentiality.

All relevant laboratory and clinical data will be abstracted by the PI and the study coordinator and coded. The linkage information will either be kept in a locked drawer in the Genome facility at UC Davis or stored on a computer not linked to the internet at that facility. All other data will be coded and individual patient identifiers will be removed. At the conclusion of data acquisition all linking material will be shredded.

4. Explain your plan for reporting adverse and serious adverse events to the IRB.

All serious AEs will be reported to the IRB within 24 hours by either the PI or the co-PI if the PI is not on campus.

5. If the study involves the use of placebo, justify why this is appropriate.

N/A

BENEFITS:

1. Address if there is a benefit to individual subjects or to the particular group or class.

No direct benefit will accrue to the individual participants other than discovering dyslipidemia in patients who may not already be aware of this risk factor. In this case patients will be directed to a treating physician. Elucidation of the mechanism of reduced HDL in patients having CKD may ultimately lead to specific treatment for this disorder, a risk factor for further loss of renal function and for vascular disease in this population.

2. Address if there is no direct benefit to the subject.

The risk is small. The principal benefit is that of establishment of a lipid disorder in individual patients. Ultimately we hope to be able to evaluate existing agents for increasing HDL in patients having CKD to affect outcome, or to design new therapy based upon our findings.

RISK-BENEFIT RATIO:

1. Address whether the risks to subjects are reasonable in relation to the benefits (note: do not state that the benefits outweigh the risks. Rather, construct a summary assessment of the relative risks (physical, psychological, economical, and legal) to participants versus the potential benefits to participants and society).

N/A

COSTS/COMPENSATION TO SUBJECTS:

1. If the study involves the possibility of added expenses to the subject or to a third party, such as an insurer (e.g., longer hospitalization, extra laboratory tests, travel) address the magnitude of those expenses and how this is justified.

N/A

2. Describe the amount and type of compensation that will be paid to subjects and how that compensation will be staged/pro-rated.

Subjects will be compensated \$50.00 once they have completed participation in the study.

DISCLOSURE OF PERSONAL AND FINANCIAL INTEREST:

1. Disclose any personal and financial interest in the research as well as the extent of personal and financial interest in the sponsor.

None

WAIVER OF INFORMED CONSENT (if applicable): N/A

If you are requesting waiver or alteration of informed consent, you are required by federal regulations to justify the following four points, for review by the IRB:

1. The research involves no more than minimal risk to the subjects.
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
3. The research could not practicably be carried out without the waiver or alteration.
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Waiver for use of Protected Health Information for Recruitment The use or disclosure of PHI involve no more than a minimal risk to the privacy of the individual based on at least the presence of the following.

Only authorized persons will be given access to the identifiers and/or data-storage devices will be encrypted and password protected; identifiers maintained in paper format will be kept in a locked area accessible by only research staff who require access.

I will destroy the identifiers at the earliest opportunity consistent with the conduct of the research unless there is a health or research justification for retaining the identifiers or as otherwise required by law.

Protected health information from this research will not be reused or disclosed to another person or entity, except as required by law, for authorized oversight of the research study, or other research for which the use or disclosure of PHI.

I will use Quick Disclosure Activity in EMR to track all medical records accessed as defined by P&P 2446.

Elements of Health Information *

Please list the specific elements of health information for which you are requesting the wavier. t

Serum creatinine, history of diabetes, use of lipid lowering medication, presence of proteinuria greater than 500 mg per day.

Reasons for the Waiver *

What specific information will this waiver cover and why do you need this wavier to be able to conduct the research?

To avoid unnecessary contact between research staff and patients who are not eligible to participate in the study. If patients are eligible they will be approached and asked to participate and if they are willing they will be asked to provide consent to enroll in the study.

TOTAL NUMBER OF COPIES REQUIRED FOR SUBMISSION TO THE IRB ADMINISTRATION:

Original plus 1 copy