ACTIVE/ADIPOSE (A Cohort Study to Investigate the Value of Exercise in ESRD/Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD)

Study Rationale

ACTIVE-ADIPOSE is a prospectively designed multi-center study of prevalent hemodialysis (HD) patients coordinated by the United States Renal Data System (USRDS) Special Studies Centers (SSCs) in collaboration with the NIH/NIDDK Division of Kidney, Urologic and Hematologic Diseases (DKUHD), the USRDS Coordinating Center (CC), and the Centers for Medicare and Medicaid Services (CMS) End-Stage Renal Disease (ESRD) Networks. It includes a purposive sample of HD patients from clinics in the Atlanta and San Francisco metropolitan areas. We proposed this design for ACTIVE-ADIPOSE because the design used in the DMMS and CDS studies was limited to information that could be obtained by patient interview or chart review and did not lend itself to more specialized measurements. In ACTIVE-ADIPOSE, bioelectrical impedance spectroscopy, waist circumference measurements, and tests of physical performance are performed at study entry. Because these measurements are not difficult or time-consuming, they have the potential to be incorporated into routine care of dialysis patients if they are found to provide useful information. In addition, due to important advances in human subjects protection and a renewed focus on privacy led by the Health Insurance Portability and Accountability Act (HIPAA), persons directly involved in research activities (e.g., individuals conducting on-site tests or questionnaires) must receive formal training in human subjects protection, and if considered "engaged" in research individuals and their institutions must comply with federal regulations aimed to protect human subjects. The process of certifying and managing research activities remotely with limited oversight is logistically difficult, if not impossible. Thus, while it might be optimal in theory to recruit study subjects from scores if not hundreds of facilities to enhance racial, ethnic, geographic and socioeconomic diversity (and to provide a fully "nationally representative sample"), such a strategy is impractical. Instead, ACTIVE-ADIPOSE focuses on a smaller number of highly committed, geographically diverse dialysis facilities, where all members of the research team are engaged by definition.

ACTIVE-ADIPOSE is designed to accomplish proposed goals of the Rehabilitation/Quality of Life, Nutrition, and Cardiovascular special studies centers, using a single cohort. This combined study concept will allow large sample sizes for each study without requiring the resources and personnel to assemble multiple cohorts. In addition, because the same patients will undergo all study interventions, a richer dataset will ultimately be available, and it will be possible to evaluate associations between nutritional and cardiac or cardiac and rehabilitation parameters, for example.

Study Synopsis

Study Subjects: ESRD patients aged ≥18 years old, English- or Spanish-speaking, undergoing maintenance HD in dialysis units located in the Atlanta and San Francisco metropolitan areas. Prior or pending transplant is not an exclusion criterion. Double amputees may participate but will not undergo BIS.

Data Collection:
Baseline:

- Medical history and laboratory data
- Results of echocardiography
- Physical activity patterns
- Activities of Daily Living (ADL)
- Center for Epidemiological Studies-Depression (CES-D)

- *Body composition*: Bioelectrical impedance spectroscopy, waist circumference
- *Physical performance tests*: grip strength, gait speed, chair stand, static balance
- *Laboratory tests*: markers of nutritional status, inflammation, and cardiac function

Follow-up:

Annually:

- Interim medical history
- Interim echocardiography results
- Interim hospitalization, institutionalization
- Referral for physical therapy or other rehabilitation program
- Physical activity, ADL instruments
- Body composition measures

Semi-annually: Laboratory nutritional status and inflammation markers, cardiac markers

Design: Prospective cohort followed for 2 years

Specific Aims

Cardiovascular:

Aim 1: To document the degree of adherence to K/DOQI Cardiovascular guidelines recommending echocardiograms in incident dialysis patients.
Aim 2: To determine the prevalence of cardiomyopathy in incident and prevalent dialysis patients in the modern treatment era.
Aim 3: To determine the extent to which echocardiographic findings predict cardiovascular morbidity and mortality among patients on dialysis.
Aim 4: To determine the extent to which cardiac and other serum biomarkers correlate with echocardiographic findings and predict cardiovascular morbidity and mortality among dialysis patients.
Aim 5: To determine the temporal variability of serum biomarkers prospectively in dialysis patients and the correlation of this variability with long-term morbidity and mortality

Nutrition:

Aim 1: To determine the strength and direction of associations among inflammatory markers, lipoproteins, adipokines, fetuin A and other factors associated with insulin resistance with body composition in hemodialysis patients.
Aim 2: To determine the rate of change in body compartments, including lean and adipose mass, in a cohort of hemodialysis patients.
Aim 3: To determine the strength and direction of associations among several methods of body composition analysis (including body weight for height indices, waist circumference and bioimpedance analysis) with mortality and hospitalization in hemodialysis patients.
Aim 4a: To determine the strength and direction of associations among inflammatory markers, lipoproteins, adipokines, fetuin A with mortality and hospitalization in hemodialysis patients.
Aim 4b: To determine whether serum concentrations of inflammatory markers, lipoproteins, adipokines, and fetuin A modify the association between body composition and mortality and hospitalization in hemodialysis patients.

Rehabilitation/Quality of Life:

Aim 1: To determine the prevalence and predictors of patient participation in physical activity.
Aim 2: To measure the association of physical activity level with change in physical functioning between baseline and follow-up.
Aim 3: To investigate the applicability and usefulness of the geriatric construct of frailty among

patients with ESRD. Specifically, to determine the association of physical activity level with the other four components of the frailty phenotype (wasting, weakness, poor energy, slowness), to determine the prevalence of patients who meet the definition of frailty based on this phenotype, and to investigate outcomes associated with the frailty phenotype.
Aim 4: To explore common barriers to physical activity participation in dialysis patients.

Study Variables and Measures

Baseline

Medical history and status
- Comorbidities, including vision status
- Medications
- Vascular access type
- Monthly labs
- Blood draw during dialysis for nutritional and cardiac markers

Patient Questionnaire – ~30 minutes; during dialysis session
- Education
- Work status, ability to work
- Patient-reported leisure-time physical activity
- Recent falls, fractures
- Weight loss over the preceding year
- SF-36 Physical Function, Vitality scales; KDQOL Cognitive Function scale
- ADL difficulty
- CES-D
- Sleep (EPESE questions)
- RLS (NIH criteria)
- Perceived barriers to physical activity

Physical performance – 15 minutes; before dialysis session
- Grip strength
- Gait speed over 15 foot level surface
- Chair stand
- Static balance

Body composition – 10 minutes; before dialysis session
- Height and weight
- Waist circumference
- BIS

1-year and 2-year Follow-ups

Interim medical history
- Hospitalization events
- Medications

Repeat patient questionnaire, physical performance and body composition assessments
Blood draw during dialysis for nutritional and cardiac markers (also at baseline + 6 months and at 1 year + 6 months)

Sample

HD patients treated in Atlanta area and San Francisco area dialysis clinics will be asked to participate in an observational, prospective cohort study. Baseline enrollment of 375 prevalent HD patients over a two-year period is targeted in each of the study areas, to yield a total of 750 HD patients enrolled at baseline. Participants will be patients aged ≥18 years old, on HD for at least 3 months and capable of

giving informed consent. Exclusion criteria include treatment by peritoneal dialysis, active malignancy, and special vulnerable populations (pregnant women, prisoners, persons with significant mental illness).

Sample Facility Enrollment

Atlanta GA metropolitan area: Emory University and DaVita dialysis facilities
San Francisco metropolitan area: Satellite dialysis facilities; VA dialysis

Patient Recruitment

A baseline enrollment of 750 prevalent HD patients is targeted. With approval of the dialysis clinic medical director, the study coordinator meets with clinic staff to explain the study. The coordinator approaches patients directly to explain the study and request their participation. Interested patients are asked to sign an informed consent, which the study coordinator reviews with the patient and answers any questions. The need to obtain protected health information (PHI), and uses that will be made of this information, are summarized in the informed consent. The informed consent also explains how patients may revoke their authorization for use of their PHI. There are no costs to patients for participating in the study. Patients can refuse to be in the study and can stop participating at any time after giving consent. The patient can also ask that his/her blood samples be withdrawn from research use, after which any identifiable samples in the investigators' possession will be destroyed. Withdrawing from the study will not affect in any way the patient's current or future dialysis care.

Data Collection from Patients:

Baseline only:

Demographics: Patients are asked their date of birth, ethnicity, race, education, and smoking history

Baseline and 2 annual follow-ups:

Patient Questionnaire: Patients are asked about their work and activity status, recent falls/fractures, recent weight loss, recent hospitalizations, perceived physical functioning and vitality, sleep/restless legs complaints, perceived cognitive functioning, depressed mood, perceived exercise barriers

Physical Performance Form: Study coordinator administers tests of patient's grip strength, walk speed, chair stand, and standing balance. Patients may use any needed assistive devices during the physical performance tests, and the coordinator closely monitors the patient's safety during these tests

Body Composition Form: Study coordinator records patient's pre-dialysis weight measured by the dialysis staff. Study coordinator measures patient's height; waist circumference; and estimated fat-free mass, fat mass, total body water, intracellular water, and extracellular water from bioimpedance spectroscopy (BIS),using ImpediMed. Body composition measures are targeted for pre-dialysis on the second or third dialysis session of the week.

Data Collection from Medical Records

Baseline only:

Medical History Form: Medical charts are reviewed to ascertain patient medical history during the last 10 years.

Baseline and 2 annual follow-ups:

Medical Questionnaire: Medical charts are reviewed to ascertain recent/current medical history, including comorbid conditions, blood pressure, dialysis prescription and compliance, routine lab values, and prescribed medications.

Retrieval and Handling of Blood Samples

Baseline and every 6 months for a total of 5 collections: For consenting patients,15 ml extra blood (12 ml tiger top tube and 3 ml purple top tube) are drawn during HD which will supply nutrition/inflammation markers and cardiac markers.

Patient Compensation

Following each annual study participation, patients receive $25 compensation for their time.

Data Entry and Quality Control

Case report forms must contain no empty data blocks. After they are checked for legibility and completeness by the Study Coordinator, case report forms are computerized at each data collection site. The Atlanta site is the location of the Data Coordinating Center, under the direction of Rebecca Zhang, Data Manager. Forms are transmitted from the San Francisco site to the Atlanta site via a secure data network. Data entry staff review and resolve with the local Study Coordinator any questions that emerge during the data entry process.

Transmission of ACTIVE-ADIPOSE Database to CC

Datasets from the Atlanta and San Francisco sites will be prepared by Rebecca Zhang, Data Manager, and transmitted to the CC in coordination with direction from Shu Chen.

Processing of Blood Samples and Transmission of Dataset to CC

Upon receipt of blood samples, A-CTSI staff will pour off the serum into a plastic tube, aliquot it, and freeze it. The frozen tubes, labeled by Study ID, are accumulated and shipped to Dr. Kaysen's lab. Analyses will take place at Dr. Kaysen's lab. Dr. Kaysen will then transmit to the CC a dataset containing the analysis results.

Coordination and Implementation of the Study

Individual study sites (Nutrition SSC, Rehabilitation/QoL SSC) shall:

- Hire local study coordinators who will recruit patients and administer baseline and follow-up data collection.
- Obtain local Institutional Review Board (IRB) approval of the study prior to enrolling subjects and maintain approval throughout the period of data collection and analysis.
- Assume responsibility for the execution of the protocol as specified in the Manual of Operations.
- Be available to respond to data quality questions and any potential problems in data collection or transmission.
- Maintain confidentiality and security of all data collected.