The moon stood still
On Blueberry Hill
It lingered until
My dreams came true

Vincent Rose & John Rooney,
"Blueberry Hill"

Chapter Nine
Nutrition, Rehabilitation/Quality of Life, and Cardiovascular Special Studies
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

ACTIVE/ADIPOSE is a prospective, multi-center study of prevalent hemodialysis patients coordinated by the United States Renal Data System (USRDS) Nutrition, Rehabilitation/Quality of Life, and Cardiovascular Special Studies Centers in collaboration with the NIH/NIDDK Division of Kidney, Urologic, and Hematologic Diseases and the USRDS Coordinating Center. Data sources include performance-based, body composition, and patient-reported measures as well as medical chart review and serum samples for nutritional and cardiac biomarkers. The study is designed to meet research objectives of each of the Special Studies Centers, and will also support investigation of associations between nutrition and cardiovascular parameters, cardiovascular and rehabilitation parameters, and nutrition and rehabilitation parameters.

BACKGROUND AND PURPOSE
REHABILITATION/QUALITY OF LIFE OBJECTIVES
Chronic kidney disease appears to be a wasting disease, but little is known about potential modifiers of loss of lean body mass or other body compartments and the role of inflammatory markers and lipid abnormalities. Limitations in physical functioning (with decreased health-related quality of life) and increased risk of hospitalization and mortality are well documented issues in dialysis patients. The concept of frailty represents reduced physiologic capacity in neurologic control, mechanical performance, and energy metabolism, which heighten an individual’s vulnerability to adverse outcomes. Rapidly accumulating evidence in the geriatric literature about factors contributing to frailty may provide important insights regarding dialysis patients’ vulnerability to wasting, impaired functional status, morbidity, and mortality.

The ACTIVE/ADIPOSE study will assess prospectively, for the first time, the prevalence of frailty characteristics in a large cohort of hemodialysis patients, will investigate change in these characteristics over two annual follow-up evaluations, and will examine the association of frailty with changes in functional status, falls, hospitalization, and mortality. With regard to clinical care, the research has important implications for monitoring and intervening on risks for frailty and for decreased functional status and quality of life in patients on hemodialysis.

The exercise tolerance of most ESRD patients is low. It is unclear whether inactivity, one frailty indicator, is the best predictor of patients’ functional decline, or whether other characteristics may better identify patients who are likely to lose physical function. Interventions geared towards increasing participation in moderate intensity physical activity could be a practicable way to address the problem of sedentary behavior in this population. Because the effects of interventions to increase moderate physical activity among patients on dialysis have not been well studied, and such programs are not widely available to dialysis patients, there is a great need for randomized trials in this area. More information is needed, however, to develop feasible interventions targeted to patients who are likely to participate and to benefit. It is vital to deter-
mine the rate of participation in physical activity among ESRD patients, the characteristics associated with higher physical activity, predictors of decline in physical performance or self-reported functioning, and predictors of the development of disability. The construct of frailty has been extensively studied in the general elderly population and found to be highly predictive of poor outcomes, but these studies have not been applied in the ESRD population.

NUTRITION OBJECTIVES

Unintentional weight loss is another indicator associated with frailty. Longitudinal studies are needed to better understand the natural history of wasting with ESRD and its implications for long-term survival. Few studies have evaluated the pace and potential modifiers of loss of lean body mass, total body water (TBW), or other body compartments. Longer dialysis vintage has been shown to be associated with lower body weight, TBW, and body cell mass, and with decline in phase angle. Cross-sectional analyses probably underestimate these changes because of a bias towards better nutrition among survivors. This study will furnish information about the composition of weight loss over time, and simultaneously measure potential determinants of wasting such as inflammatory markers.

Higher body mass index (BMI) is associated with improved survival among patients with ESRD. This finding is contrary to the increased mortality seen among obese individuals in the general population, and is particularly puzzling because obesity is generally associated with insulin resistance, lipid alterations, and other factors that increase the risk of cardiovascular death, the major cause of death among patients with ESRD. There are many potential explanations for the apparently protective effect of high body fat among patients with ESRD, including 1) misclassification related to estimates of obesity based solely on height and weight, 2) starvation “protection” as a result of increased energy reserves in the form of higher body fat, 3) a “survivor bias” in the years leading up to ESRD, and 4) a diminished or paradoxical effect of obesity and its metabolic correlates in the setting of uremia. A major goal is to systematically evaluate the contributions of these factors to the observed survival advantage of higher BMI.

Data from ACTIVE/ADIPOSE will be useful for investigating whether baseline adiposity is associated with survival and other outcomes. Longitudinal body composition data can be used to determine whether baseline adiposity is associated with mitigation of wasting in dialysis patients, and will facilitate evaluation of the relations among adiposity, adipokines, fetuin A, Matrix gla protein and other factors associated with insulin resistance, vascular calcification, and cardiovascular outcomes in hemodialysis patients.

CARDIOVASCULAR OBJECTIVES

Compared to normal subjects, dialysis patients appear to be chronically in higher inflammatory states, as suggested by high serum levels of CRP and pro-inflammatory cytokines. While inflammation is a source of oxidative stress, and high serum CRP levels have been associated with higher mortality in dialysis patients (including those without documented ischemic heart disease), it is unclear which inflammatory mechanisms are involved and how
they are related to specific types of cardiovascular disease (e.g., coronary artery disease vs. cardiomyopathy). In the general population, an array of biomarkers reflecting critical components of the inflammatory pathway resulting in atherosclerotic plaque instability and myocardial necrosis has been related to clinical outcome. For example, the release of troponin from the myocardium has been used to provide risk stratification for patients with known chronic coronary artery disease and those presenting with asymptomatic coronary syndrome. It is important to identify biomarkers that predict both coronary artery disease and plaque rupture, and to examine the relationship of these biomarkers to long-term all-cause and cardiovascular mortality. Non-fatal cardiovascular events such as AMI and CHF hospitalization, and their association with biomarkers, can also be examined. The association between biomarkers and echocardiographic findings in active/ adipose will be examined at baseline and follow-up, and the study will facilitate relational studies of biomarkers, demographic variables including race and gender, comorbid medical conditions, medication use, and long-term morbidity and mortality.

**Design**
Prospective cohort study with two annual follow-ups and semi-annual blood draws, initiated in the fall of 2009.

**Data collection sites**
- Atlanta GA metropolitan area: dialysis clinics affiliated with Emory University and DaVita, Inc.
- San Francisco CA metropolitan area: dialysis clinics affiliated with the San Francisco VA, San Francisco General Hospital, the University of California San Francisco, Satellite Healthcare Inc., and Renal Advantage, Inc.

**Patients**
Baseline target enrollment of 750 prevalent hemodialysis patients, accumulated over a two-year period. Participants are age 18 or older, English- or Spanish-speaking, on hemodialysis for at least three 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). Prior or pending transplantation is not an exclusion criterion. Double amputees may participate, but do not undergo bioelectrical impedance spectroscopy (BIS).

**Data sources and measures**
- **From patients**
  - Baseline only
    - **Demographics** Patients are asked their date of birth, ethnicity, race, highest education level completed, and smoking history.
    - **Patient questionnaire** Patients are asked about their work and activity status, living situation, current smoking status, receipt of rehabilitation services, recent falls/fractures, recent weight loss, recent hospitalizations, perceived physical functioning and vitality, nocturnal sleep quantity and quality, restless legs complaint, perceived cognitive functioning, depressed mood, and perceived exercise barriers.
  - Baseline and two annual follow-ups
    - **Medical history** Medical charts are reviewed to ascertain recorded history of coronary heart disease or coronary artery disease, other heart disease, cerebrovascular disease, peripheral artery disease, diabetes, lung disease, amputation, neoplasms, and other conditions (peptic ulcer disease, recurrent GI blood loss, chronic arthritis, vision problems, periodontal disease, HIV, AIDS).

**From medical records**
- Baseline only
  - **Medical history** Medical charts are reviewed to ascertain recorded history of coronary heart disease or coronary artery disease, other heart disease, cerebrovascular disease, peripheral artery disease, diabetes, lung disease, amputation, neoplasms, and other conditions (peptic ulcer disease, recurrent GI blood loss, chronic arthritis, vision problems, periodontal disease, HIV, AIDS).

**Novel measures that will be available from active/adipose**
- **Frailty** Clinical syndrome defined by weight loss in the last year; exhaustion; low physical activity; slow walk time; low grip strength (Fried et al., J Gerontol Med Sci 56A: M146–M156, 2001).
- **Short physical performance battery** Lower extremity function defined by balance, gait, strength, and endurance measured by standing balance, walk time, and chair rise (Guralnik et al., J Gerontol Med Sci 54:M85–M94, 1999).
- **Estimated fat-free mass, fat mass, total body water, intracellular water, extracellular water** Bioimpedance spectroscopy measurements from ImpediMed 8177 Body Composition Analyzer.