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CRC Research Protocol
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Title of protocol: Mortality and ESRD among Obese Patients with CKD stage 3-4: Is the Burden Higher for African Americans?

1. Study Purpose and Rationale.

Over the last three decades, obesity prevalence has more than doubled among U.S. adults. In the most recent National Health and Nutrition Examination Survey (NHANES), 33.8% of U.S. adults met the clinical criteria for obesity with a body mass index (BMI) $\geq$30 kg/m2 (1). The rising prevalence of obesity has been matched by a parallel increase in the prevalence of metabolic syndrome. (2). Of equal concern is the rising rate of chronic kidney disease in this country – since the early 1990s, the overall prevalence of chronic kidney disease (CKD) stage 1 through 4 has increased from 10 to 13% (1).

The correlation between CKD and components of metabolic syndrome – such as hypertension and diabetes, has been well established for years, and recently a growing body of evidence has emerged suggesting that obesity by itself – *independent* of its association with those comorbidities – is a key player in renal injuries (3-8). The association between obesity and CKD appears to be multifactorial and may be mediated by altered mechanical forces, chronic inflammation, abnormal vascular remodeling, renal lipotoxicity, and by a disordered relationship between volume status and aldosterone secretion (9). There is some data suggesting that this pathophysiology of obesity related kidney damage may also be more pronounced in African-Americans, an ethnic group with high prevalences of hypertension, obesity, and aggressive CKD (10-13).

According to the most recently published data by US Renal Data System, in 2007, the rate of new ESRD cases among African Americans was noted to be 3.7 times the rate among whites (998 versus 273 per million population - controlling for age, sex and co-morbidities). The prevalence of ESRD was also noted to be 4.2 times higher among the African Americans (rate of 5,111 prevalent ESRD cases per million population among African Americans versus rate of 1,231 among whites) (14). Higher incidence of ESRD among blacks appears to be due faster rate of progression from CKD to ESRD and not just due to difference in prevalence of CKD in the two populations (15).

Unfortunately there has been a paucity of data on changes in CKD over time and correlation with changes in incidence of ESRD. One cohort study showed that African Americans, who at baseline had worse proteinurea and BP control, were five times more likely to progress to ESRD than their white counterparts (15). Another study, a secondary analysis of African American Study of Hypertension and Kidney Disease, looked at African Americans with and without metabolic syndrome and CKD, and showed that those who met the criteria for metabolic syndrome had worse proteinurea at baseline and were 31% more likely to reach GFR decrease of 50%, ESRD or death within the average four years of follow up (16).

Bomback et al recently analyzed data from the National Kidney Foundation's Kidney Early Evaluation Program (KEEP), a community based health screening program (17). In that analysis of >37,000 obese participants at risk for kidney disease presenting for voluntary screening, whites tended to have more metabolic syndrome components and more profoundly decreased eGFRs than African Americans (CKD 3-5 prevalence 23.6% vs. 13.0%, $p<0.001$). African Americans on the other hand were noted to have more evidence of early CKD stages with worse abnormal urinary albumin excretion. Among those with CKD stages 3-5 (1,483 whites and 547 blacks) anemia prevalence was 32.4% in African Americans compared to 14.1% in whites, prevalence of secondary hyperparathyroidism was 66.2% and. 46.6% respectively. Given that data, an argument can be made for obesity and metabolic syndrome being heterogeneous disease states in African Americans and whites (17).

To evaluate that further, given that the 10 year anniversary for the KEEP screening is approaching, we would like explore whether the differences observed in the cross-sectional analysis mentioned above translate into disparate rates of kidney disease progression and mortality burden among the two groups during long term follow up. The key question we want to answer is whether the rates of ESRD and death are different for obese blacks vs. obese whites with CKD 3-4. If we control for comorbidities (presence of DM, HTN), age, sex, tobacco/alcohol use, family history of CKD, insurance status, education level, baseline laboratory findings (hemoglobin, PTH, calcium, phosphate level), and degree of albuminuria at time of the screen, and still detect a difference between the two cohorts, the study will provide more evidence for a biological mediator for the discrepancy between incidence and prevalence of ESRD in African Americans compared to whites.

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2. Study Design and Statistical Procedures

The study will be a nested case control study within prospective cohort.

The study will include two cohorts drawn from KEEP participants screened between August 2000 and August 2010. The first cohort will include eligible KEEP participants with BMI $\geq$ 30 kg/m^2 that reported their race as "white" and were noted to have calculated eGFRs between 60ml/min/1.73m^2 and 15ml/min/1.73m^2 (CKD stage 3-4). The second cohort will include all those who self identified as "African American" and had those same pre-existing conditions on screening (BMI $\geq$ 30 kg/m^2 and CKD stage 3 to 4).

We will request data from the KEEP dataset from 2000 through 2010 for analysis.

Baseline variables to be assessed include:

- Age
- Gender

- Race
  - White
  - Black
- Level of Education
  - < High school
  - High school graduate
  - College graduate
  - Professional degree
- Current tobacco use
- Current alcohol use
- Body Mass Index
- Waist circumference
- Systolic blood pressure
- Diastolic blood pressure
- Hypertension
  - average systolic blood pressure >130 mm Hg or diastolic blood pressure > 80 mm Hg
  - a self-reported history of hypertension,
  - patients taking blood pressure lowering medication
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- Dyslipidemia
  - a fasting triglyceride level above 150 mg/dl or high density lipoprotein level (HDL) less than 40 mg/dl (men) or under 50 mg/dl (women) (ATP III criteria),
  - a self-reported history of dyslipidemia,
  - patients taking lipid lowering medication.
- Fasting blood glucose
- Diabetes Mellitus
  - a fasting blood glucose (sugar) level greater than 126 mg/dL
  - a self-reported history of diabetes mellitus,
  - patients taking glucose lowering medications.
- Albumin:creatinine ratio
  - Normal: <30 mg/g
  - Microalbuminuria: 30-300 mg/g
  - Macroalbuminuria: >300 mg/g
- Serum creatinine (by the Cleveland Clinic Research Laboratory)
- Estimated GFR
- Stages of CKD based on eGFR calculated using the 4 variable MDRD equation
  - No CKD: eGFR (MDRD) > 59 ml/min/1.73m^2 and no proteinuria
  - Stage I: eGFR (MDRD) >= 90 ml/min/1.73m^2 and microalbuminuria
  - Stage II: eGFR 60-89 ml/min/1.73m^2 and microalbuminuria
  - Stage III: eGFR (MDRD) 30-59 ml/min/1.73m^2
  - Stage IV: eGFR (MDRD) 15-29 ml/min/1.73m^2

    - Stage V (ESRD): eGFR (MDRD) < 15 ml/min/1.73m^2
- Family history of kidney disease
- Family history of HTN
- Family history of DM
- Insurance status

In Dec of 2010, we will request the KEEP Data Coordinating Center to run a cross-check for us between our cohort participants identifying data (name, social security) and current national registries of ESRD and death.

All-cause mortality will be determined by using a previously validated multilevel tracking system by the Chronic Disease Research Group at Minneapolis Medical Research Foundation, Hennepin County Medical Center, (or if that is unattainable, we will use that available through the US Renal Data System Coordinating Center). The system is capable of using name and social security number data and linking that to incident end-stage renal disease patient records (present in USRDS), with cross-checks against the US Medicare database and Social Security Administration Death Files

We will use a chi-square analysis to determine if any difference exists between the rates of mortality and ESRD between the African Americans and whites with obesity and CKD stage 3-4 within the 10 year follow up available to us. Time-to-event (ESRD and death) will be calculated for all patients and plotted on a Kaplan Meir curve adjusting for exposure time. Cox proportional hazards analysis will be implemented to adjust for baseline covariates - age, gender, presence of diabetes and/or hypertension, systolic and diastolic blood pressure on screening, dyslipidemia, family history of kidney disease, education level, and insurance status. In the multivariate analysis we will also adjust for BMI and stratify data by two subgroups– those with BMI between 30-35 and those with BMI over 35. The study we are working off of suggested that BMIs were significantly higher among African Americans who met criteria for obesity than whites – 36.6kg/m^2 versus 35.9kg/m^2 respectively.

Power analysis:
If we assume that about 15% will progress to ESRD or death within 10 years (given that some studies suggest that on average those with CKD 3-4 progress to ESRD at a rate of 1.5%/year, and mortality data is quite varied – between 3 to 10% depending on the study)

And we will likely have an n of approximately 2000 in the white cohort and ~750 in the African American cohort,

We will be able to detect with 80% power and alpha of 0.05, if African Americans have a rate that is greater than 20% or less than 11%.

3. Study Procedures

The investigation will compare mortality and ESRD incidence among black and white obese (BMI>30) participants in the KEEP who were found to have baseline CKD stage 3-4 during screening up to 10 years ago. With simple chi square analyses, we will compare the rates of death and ESRD among our two cohorts (by linking data from KEEP to USRDS data on ESRD patients and US Medicare Database and Social Security Administration Death files for mortality data. We will plot Kaplan Meir curves for our two cohorts and use Cox regressional analysis to assess covariates.

Specific Aims

1. **To determine whether obese African Americans with CKD stage 3-4 progress to death or ESRD faster than their white counterparts.**

4. **Study Drugs or Devices**

N/A

5. **Study Questionnaires**

N/A

6. **Study Subjects.**

A) Inclusion Criteria

1. All subjects submitted to KEEP screening >18 years of age with body mass index (BMI) $\geq$30 kg/m^2 and CKD stage 3-4

B) Exclusion criteria (based on KEEP data)

2. All subjects who report Hispanic or Latino origin (question 5)
3. All subjects who report a race other than "white" or "black" (question 6)
4. All subjects who have normal renal function or CKD 1-2, or CKD 5
5. All subjects who have reported being on dialysis or having a kidney transplant (questions 12 and 13)

7. **Recruitment**

N/A – patients already recruited during voluntary screening

8. **Confidentiality of Study Data**

The study investigators will have no access to identifiable data – the KEEP Data Coordinating Center will run the cross-check analysis and provide us with de-identifiable data.

9. **Potential Risks**

There are no identifiable physical or emotional risks to the study participants. The participants have volunteered for screening in the past. As there will be no identifiable data linking participants to the end points or any of our analysis, there should be no risks posed to them.

10. **Potential Benefits**

There are no direct benefits for subjects participating in this study. The potential benefit of the study includes better understanding of the rates of kidney disease progression and mortality burden between obese whites and African Americans.

11. Alternatives
N/A