# ARIC Manuscript Proposal # 3322

PC Reviewed:  1/8/19          Status: _____          Priority: 2
SC Reviewed: _____        Status: _____          Priority: ____

**1.a.  Full Title**:
Retinopathy and risk of kidney disease in persons with diabetes

**  b.  Abbreviated Title (Length 26 characters)**:
Retinopathy and kidney disease in diabetes

**2.     Writing Group**:
Writing group members: Jingyao Hong, Elizabeth Selvin, Morgan Grams, Josef Coresh, Shoshana Ballew, Natalie Daya, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___JH__ **[please confirm with your initials electronically or in writing]**

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**3.     Timeline**:
The study and article preparation would be completed in 9 months.

**4.     Rationale**:

Diabetes is a growing health concern. An estimated 425 million people had diabetes worldwide in 2017, and the number is predicted to rise to 693 million by 2045.[1]

Chronic kidney disease is one of the common complications of diabetes.[2] According to a report by the CDC, 36.5% of adults with diagnosed diabetes in the United States will develop CKD (stage 1-4).[3] Studies have indicated that loss of the glomerular and peritubular capillary microvasculature, partly due to imbalanced expression of angiogenic factors in the kidney, is associated with the development of glomerular and tubulointerstitial scarring.[4] This mechanism is also believed to underlie pathology of retinopathy in diabetes. Indeed, a classic belief is that diabetes-associated retinopathy is a necessary precedent to diabetes-associated nephropathy. However, studies evaluating the association between retinopathy and kidney disease have been somewhat inconsistent. Some observed a positive relationship between retinopathy and CKD progression,[5,6,7] while a few reported a null association.[8,9] Moreover, the studies were heterogeneous in terms of type of diabetes,[9] ethnicity[10,11].

We propose to expand on these studies, which include two performed in the ARIC cohort reporting an association of retinal abnormalities assessed at visit 3 with risk of CKD developing at visit 4.[12,13] In particular, we will assess the independent association of retinopathy with incident CKD and ESKD over and above known risk factors, including albuminuria. We will evaluate whether including retinopathy in the kidney failure risk equation adds additional discrimination to prediction of ESKD among participants with eGFR <60 ml/min/1.73 m2, and we will compare the strength of association between retinopathy and ESKD with that between retinopathy and incident CVD.

The kidney failure risk equation (KFRE) is a tool developed to predict the probability of kidney failure, using age, sex, eGFR and urine albumin to creatinine ratio. KFRE has been validated in several cohorts and is widely used to help guide dialysis and kidney transplant.[14] However, it may be that it can be improved upon with additional disease-specific information in the setting of diabetes. We would further evaluate the validity of KFRE and assess the improvement of including retinopathy to the KFRE for predicting risk of kidney failure among individuals with diabetes.

## 5.    Main Hypothesis/Study Questions:

1. What is the cross-sectional association of kidney disease and retinopathy in persons with diabetes?
Our hypothesis is that the proportion of people with diabetes and kidney disease who have retinopathy is similar across sex and higher with longer duration of diabetes.
2. Is retinopathy a risk factor for subsequent development of kidney disease in persons with diabetes?
Our hypothesis is that retinopathy is associated with kidney disease onset and progression above known risk factors such as age, sex, eGFR and albuminuria.
3. Is retinopathy a risk factor for cardiovascular outcomes in persons with diabetes?
Our hypothesis is that retinopathy is related to future cardiovascular events but that the strength of association is weaker than that of the association with ESKD.
4. Does the inclusion of retinopathy improve the discrimination of the KFRE in the setting of CKD and diabetes?
Our hypothesis is that retinopathy improves the discrimination of the KFRE in the setting of CKD and diabetes.

**6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

**Study design**
Our study will include (1) A cross-sectional study of persons with diabetes at visit 4. (2) A prospective cohort study with baseline at visit 4 among patients with diabetes but no prevalent eGFR <60 (for evaluation of incident eGFR <60) and no prevalent ESKD (for evaluation of ESKD). In the comparison of associations between retinopathy and ESKD and retinopathy and CVD, visit 4 participants with either ESKD or a history of CVD will be excluded. For the evaluation of the KFRE, participants with GFR <60 will be included. In sensitivity analysis, we will look at the association between retinopathy and kidney outcomes in participants without diabetes.

**Population**
We will include participants who have retinopathy photographs taken at visit 3 and who have prevalent diabetes at visit 4.

**Exposure**
Retinopathy will be defined based on retinal images taken at visit 3. One 45° non-stereoscopic color retinal photograph of one eye of each participant was taken. Photographs were then assessed by masked graders using the Modified Airlie House Classification of Diabetic Retinopathy. A retinopathy severity score was assigned based on the presence of various lesions: level 10, none; level 20, minimal nonproliferative retinopathy (microaneurysms only or blot hemorrhages only); level 35, early nonproliferative retinopathy (microaneurysms and one or more of the following: venous loops, soft exudate or hard exudate, and questionable intraretinal microvascular abnormalities or venous beading); levels 43 to 47, moderate to severe nonproliferative retinopathy (microaneurysms and one or more of the following: intraretinal microvascular abnormalities, venous beading, hemorrhages, and microaneursyms exceeding those in standard photograph 2A); level 60+, proliferative retinopathy.[15,16]

**Outcomes**
Kidney disease will be defined as a hospitalization with CKD diagnostic code or GFR <60 ml/min/1.73m$^2$ at a subsequent visit. Incident ESRD will be defined by linkage with the USRDS database. Serum creatinine was measured at visit 4, 5, 6 and would be applied to calculate estimated GFR. Risk of kidney failure will be calculated based on the kidney failure risk equation (KFRE) using participant's age, sex, eGFR and the ratio of urine albumin to creatine levels.
Cardiovascular outcome will be defined as first onset of incident coronary heart disease (CHD) events occurring after visit 4.

**Covariates**
Kidney markers: estimated GFR and ACR
Socio-demographic characteristics: age (continuous), sex, race-center (excluding non-white, non-African American)

Risk factors: fructosamine and glycated albumin, insulin use, duration of diabetes, systolic blood pressure, diastolic blood pressure, history of hypertension, use of anti-hypertension medication, high-density lipoprotein, body mass index (BMI), smoking status, alcohol consumption

**Stratification**
In sensitivity analysis, analyses will be stratified by sex. We will also evaluate for differences in association by presence or absence of albuminuria, defined as ACR >30 mg/g.

**Statistical analysis**

**Study question #1** the cross-sectional association of kidney disease and retinopathy in persons with diabetes
A Cross-sectional analysis will be applied to the population with diabetes at visit 4, using logistic regression to assess the association of retinopathy with categories of kidney disease, as classified by GFR level, and categories of albuminuria, as classified by ACR.
A table 1 will also include characteristics including age, sex, race-center, BMI, smoking status, history of hypertension or anti-hypertension medication, systolic blood pressure, fructosamine and glycated albumin levels, insulin use, and duration of diabetes would be presented by the presence of retinopathy and compared by chi-squared and t-tests.

**Study question #2** Is retinopathy a risk factor for subsequent development of kidney disease in persons with diabetes?
A Cox proportional hazard model will be applied to estimate the hazard ratios of CKD hospitalization/incident CKD and ESRD associated with retinopathy in participants who have diabetes.
The following models will be applied:
Model A: unadjusted
Model B: demographic-adjusted
Model C: Model B further adjusted for BMI, smoking status, history of hypertension or anti-hypertension medication, kidney measures, total cholesterol, statin.
Model D: Model B further adjusted for BMI, smoking status, history of hypertension or anti-hypertension medication, kidney measures, total cholesterol, statin, fructosamine and glycated albumin levels, insulin use, and duration of diabetes.

**Study question #3** Is retinopathy a risk factor for cardiovascular outcomes in persons with diabetes?
A Cox proportional hazard model will be applied to estimate the hazard ratios of incident cardiovascular events associated with retinopathy in participants who have diabetes.
The following models will be applied:
Model A: unadjusted
Model B:  demographic-adjusted
Model C: Model B further adjusted for BMI, smoking status, history of hypertension or anti-hypertension medication, kidney measures, total cholesterol, statin.
Model D: Model B further adjusted for BMI, smoking status, history of hypertension or anti-hypertension medication, kidney measures, total cholesterol, statin, fructosamine and glycated albumin levels, insulin use, and duration of diabetes.

We can compare the strength of association between retinopathy and kidney outcomes with that of retinopathy and CVD outcomes using seemingly unrelated regression.

**Study question #4** Does the inclusion of retinopathy improve the discrimination of the KFRE in the setting of CKD and diabetes?

To evaluate the accuracy of KFRE, we will develop a model using logistic regression to estimate the 5-year risk of ESKD using the variables in the KFRE (age, sex, eGFR, ACR) with and without the addition of retinopathy. We will compare the two models, and evaluate discrimination of both using AUC.

**7.a.  Will the data be used for non-CVD analysis in this manuscript? _____ Yes   __x__ No**

  **b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? __ __ Yes   _____ No**
(This file ICTDER has been distributed to ARIC PIs, and contains
the responses to consent updates related to stored sample use for research.)

**8.a.  Will the DNA data be used in this manuscript? _____ Yes   __x__ No**

**8.b.  If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? _____ Yes   _____ No**

**9.   The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.**
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:  http://www.cscc.unc.edu/ARIC/search.php

   ___x___ Yes   _____ No

**10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

MP #1539. Hemoglobin A1c (HbA1c) Cut-points and Risk of Kidney Disease and Prevalent Retinopathy. Selvin E.
MP #2604. Systematic review and individual participant meta-analysis of the association between retinal vessel caliber and Chronic Kidney Disease. Sabanayagam C.
MP #3027. Multi-Ethnic Genome-wide Association Study of Diabetic Retinopathy using Liability Threshold Modeling of Duration of Diabetes and Glycemic Control. Pollack S.

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes ___x_ No**

**11.b. If yes, is the proposal**
     ___    **A. primarily the result of an ancillary study (list number\* _____ )**
     ___    **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)\* _____ _____ _____ )**

\*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

**12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

**13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication.** Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __x__ No.

**References**

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