ARIC Manuscript Proposal #2392

PC Reviewed: 7/8/14 Status: A Priority: 2
SC Reviewed: ________ Status: _____ Priority: _____

1.a. Full Title: Association between plasma testosterone and the incidence of diabetes and diabetic complications in the Atherosclerosis Risk in Communities (ARIC) cohort study

b. Abbreviated Title (Length 26 characters): T and Diabetes

2. Writing Group:

Writing group members: Reshmi Srinath, MD; Sherita Hill Golden, MD, MHS; Kathryn A. Carson, ScM; Adrian Dobs, MD, MHS

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

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3. **Timeline:** Data analysis will begin immediately with expected completion within 12 months.

4. **Rationale:**
The overall goal of this proposal is to understand the relationship between endogenous testosterone level and the risk of diabetes and diabetic complications in males. Coronary heart disease is considered a leading cause of death with earlier onset and possibly greater mortality in males (Murphy et al. Nat Vital Stat 2013). Those with diabetes have a two to four fold increased risk of cardiac disease and associated mortality (CDC). Testosterone has been implicated in the development of CHD and associated risk factors. Prior longitudinal studies including the Rancho Bernardo study, NHANES III, and the Massachusetts Male Aging study show that low testosterone is independently associated with the development of insulin resistance and type II diabetes mellitus in men (Oh, J et al. 2002; Selvin E et al. 2007; Kupelian E. et al. 2006), with few studies assessing the role of testosterone in predicting diabetic complications. Conversely, men with diabetes mellitus are also more likely to have low testosterone, due to changes in body composition with increased fat mass, decreased sex hormone binding globulins, increased aromatase activity leading to testosterone conversion to estrogen, and increased inflammatory mediators (Kalyani R, Dobs A 2007). Given this bi-directional relationship, more research is needed to determine how to treat men with androgen deficiency in the context of diabetes mellitus. In our study we hope to look at the distribution of serum testosterone in males and assess the relationship prospectively with incident type II diabetes mellitus and prediabetes, and associated diabetic complications independent of other cardiac risk factors.

5. **Main Hypothesis/Study Questions:** Low serum testosterone is associated with increased risk of diabetes and complications including microalbuminuria and retinopathy.

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:* Prospective cohort study, using ARIC visit 4 as baseline

*Inclusion criteria:* male ≥ to age 55 at visit 4, no prior history of coronary heart disease or ischemic stroke at baseline (ARIC Visit 4), no prior exposure or exposure during the course of the study through the last follow up to exogenous testosterone based on review of medications performed at baseline and follow up visits.

*Exclusion criteria:* females, males <age 55, known prior history of coronary disease or ischemic stroke at baseline (ARIC Visit 4), exposure to exogenous testosterone prior to or during the course of the study as assessed by review of medications performed at baseline and follow up visits, prior history of diabetes or prediabetes at baseline visit 4, prior
albuminuria (urine microalbumin/creatinine >30 mg/g) or kidney disease (GFR<60) at baseline visit 4, prior history of retinopathy (photographs) at visit 4.

Data to be collected: Plasma samples were requested from frozen samples taken from participants during visit 4 (1996-1999). We have limited our analysis to those samples taken from males before 10:30 AM with sufficient volume for laboratory analysis (>0.5 cc). Plasma total testosterone using liquid chromatography mass spectrophotometry was performed in 2012 by Dr. Shallender Bhasin (Boston University, Boston, MA).

Primary outcome: Incidence of type II diabetes mellitus with annual surveillance through 2013 OR defined by elevated fasting glucose above 126 mg/dL, elevated random glucose >200 mg/dL, self-reported physician diagnosis of diabetes, use or oral hypoglycemic medication or insulin or measured HA1C >6.5% at visit 5. Incidence of prediabetes defined by fasting glucose 100-126 mg/dL and HA1C 5.7-6.4% obtained at visit 5 (2011-2013). Secondary outcomes include incidence of insulin resistance as measured by homeostasis model assessment (HOMA) in those not on diabetic agents; incident albuminuria defined by urine microalbumin/creatinine ratio >30 mg/g and incident retinopathy based on retinal photographs taken at visit 5.

Other covariates: Age, race/center, smoking status, adiposity (waist circumference, body-mass index), fasting LDL, triglycerides, HDL, use of anti-lipid medications, hypertension status.

Analysis:
- Correlation analyses and chi-square tests respectively will be used to determine the association between morning plasma testosterone and the following measures: age, race/center, smoking status, adiposity (waist circumference, body-mass index), fasting LDL, triglycerides, HDL, use of anti-lipid medications, hypertension status.
- Proportional hazards regression analysis will be used to assess the relationship between morning plasma testosterone and incidence of diabetes and prediabetes through visit 5. Models will be adjusted for age, race/center, smoking status, BMI, waist circumference, LDL, triglycerides, and HDL, use of anti-lipid medications, hypertension status.
- Logistic regression analysis will be performed to assess the relationship between morning plasma testosterone with incidence of insulin resistance as measured by homeostasis model assessment (HOMA), incidence of albuminuria, incidence of retinopathy (retinal photographs) assessed at visit 5. Models will be adjusted for age, race/center, smoking status, BMI, waist circumference, LDL, triglycerides, and HDL, use of anti-lipid medications, hypertension status.

Data analysis will be conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC)
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 ICTDER03 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”?  
   _x___ 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.cscs.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)?

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

11.b. If yes, is the proposal  
   _X  A. primarily the result of an ancillary study (list number* 2008.01, 
       2011.02)  
   ____ 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.csc.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.

References:


