ARIC Manuscript Proposal #2193

PC Reviewed: 8/13/13 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status:** **Priority: ____**

1.a. Full Title: Thyroid dysfunction and risk of chronic kidney disease

b. Abbreviated Title (Length 26 characters): thyroid and kidney function

2. Writing Group:
Writing group members: Ulla T Schultheiss; Elizabeth Selvin; Morgan Grams; Michael Steffes; Josef Coresh; Anna Kottgen; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. UTS

First author: **Ulla T Schultheiss**
Address: University Hospital Freiburg
Department of Medicine IV
Renal Division
Berliner Allee 29
79110 Freiburg im Breisgau
Germany

Phone: 0049-761-270-78210 Fax: 0049-761-270-78040
E-mail: ulla.schultheiss@uniklinik-freiburg.de

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Anna Kottgen
Address: University Hospital Freiburg
Department of Medicine IV
Renal Division
Berliner Allee 29
79110 Freiburg im Breisgau
Germany

Phone: 0049-761-78050 Fax: 0049-761-78040
E-mail: anna.koettgen@uniklinik-freiburg.de

3. Timeline:

We aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal.

4. Rationale:

Chronic kidney disease (CKD) is increasingly recognized as a global health problem and often caused by diabetes and/or hypertension. Still the conditions leading to CKD, the health impact of CKD and its prognosis differ markedly between affected individuals (1). The high costs and poor outcomes of treatment pose a worldwide public health threat. It is estimated that by 2030, more than 2 million people in the United States will need dialysis or transplantation for kidney failure (2). Currently, the incidence of kidney failure is nearing 400 cases per million in the USA (3). Therefore the identification of factors for a better understanding and management of CKD is of high scientific priority.

Thyroid hormones (TH) are essential for an adequate growth and development of many organs, including the kidney. For example children with congenital hypothyroidism have reduced renal mass and a higher prevalence of renal and urological abnormalities (e.g. dysplastic kidney, renal agenesis) (4). Conversely, the kidney is not only an organ for metabolism and elimination of TH, but also a target organ of some of the iodothyronines' actions. Thyroid dysfunction causes remarkable changes in glomerular and tubular function and electrolyte and water homeostasis (5) as well as renal hemodynamics (6). Hypothyroidism is accompanied by a decrease in glomerular filtration, hyponatremia, and an alteration of the ability to excrete water. High concentrations of TH generate an increase in glomerular filtration rate and renal plasma flow. In hyperthyroidism there is also a resetting of the pressure-natriuresis relationship related to hyperactivity in the renin-angiotensin system, which contributes to the arterial hypertension associated with this endocrine disease (6). Several studies have shown that hyperthyroid rats have increased proteinuria, which is consistent with the presence of proteinuria in patients with Graves' disease (7). Since this proteinuria is unaffected by antihypertensive therapy, hyperthyroidism may have a direct effect on the kidney, possibly increasing the permeability of the glomerular barrier attributable to a minimal change nephropathy (8). Subclinical primary hypothyroidism has been identified as a strong predictor of all-cause mortality in chronic dialysis patients and as a risk factor for nephropathy (9, 10). There is, however, limited quantitative evidence regarding the prevalence of subclinical primary hypothyroidism in large samples of individuals, at different levels of estimated glomerular filtration rate (eGFR) (11, 12).

Renal disease, in turn, leads to significant changes in thyroid function. The association of different types of glomerulopathies with both hyper- and hypofunction of the thyroid has been reported. Less frequently, tubulointerstitial disease has been associated with functional thyroid disorders. Nephrotic syndrome is accompanied by changes in the concentrations of TH due primarily to loss of protein in the urine. Acute kidney injury and chronic kidney disease (CKD) are accompanied by notable effects on the hypothalamus–pituitary–thyroid axis. The secretion of pituitary thyrotropin (TSH) is impaired in uremia (13). There is a relationship between plasma concentration of triiodothyronine (T3) and inflammation (elevated concentrations of hsCRP, interleukin 6, vascular adhesion molecule-1), nutritional status (decrease of albumin and IGF-1) and

endothelial activation in patients with CKD (14). The lower the concentration of T3, the greater the degree of inflammation. Therefore, low T3 is associated with a survival disadvantage leading to increased cardiovascular mortality in euthyroid CKD patients (14). This makes T3 a potentially interesting marker for the prediction of mortality in patients with CKD.

In the general population, the National Health and Nutritional Examination Survey (NHANES) III survey reported positive thyroid peroxidase antibody *(*TPOAb) concentrations in 10% of the general population very often indicating autoimmune thyroiditis. Concentrations of TPO-Ab have not yet been well defined for patients with incident CKD or kidney function decline and the association between autoimmune thyroiditis and the development of CKD (15).

All in all relatively little is known about the prevalence or severity of thyroid abnormalities in persons with incident CKD as compared to individuals who do not develop CKD, or about the association between thyroid abnormalities and kidney function decline.

5. Main Hypothesis/Study Questions:

The overarching objectives of this study are to characterize

1) the serum concentrations of thyroid function measures and the prevalence of thyroid disorders across different levels of renal function at the ARIC baseline visit (visit 2) and
2) the association of thyroid hormones with incident renal endpoints (CKD, ESRD, kidney failure, AKI) and kidney function decline in the community-based ARIC Study. We will further assess the effect of hypothyroidism, hyperthyroidism, subclinical hypothyroidism, low T3 and autoimmune thyroiditis on the development of renal endpoints and kidney disease-related complications.

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:

Measures of thyroid function were assayed in 2012-2013 from all participants with stored blood samples available at the second ARIC examination (Ancillary Study #2009.24, PI: Selvin). Thus, the baseline for the present study will be visit 2 (1990-1992), where measures of thyroid function (TSH, FT4, T3, anti-TPOAb) and biomarkers of kidney function are both available. Prospective cohort analysis will evaluate new onset renal endpoints occurring after ARIC visit 2.

Thyroid function and renal function parameters, thyroid and kidney disease:

Standard values of thyroid parameters:

The normal range of TSH is 0.3 - 4.5 mU/L; of fT4 10.6 – 22.7 pmol/L; and of T3 3.4 – 6.8 pmol/L.

Thyroid-stimulating hormone (TSH, thyrotropin)
Thyroid-stimulating hormone was measured in 2012-2013 in serum on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation) using a sandwich immunoassay method (Roche Diagnostics, Indianapolis, IN 46250). The laboratory CVs were 7.6% at a concentration of 0.195 mIU/L and 4.5% at a concentration of 1.98 mIU/L.

Thyroxine, free (FT4)
Thyroxine (free) was measured in 2012-2013 in serum on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation) using a competition immunoassay method (Roche Diagnostics, Indianapolis, IN 46250). The laboratory CVs were 4.2% at a concentration of 1.22 ng/dL and 4.5% at a concentration of 2.84 ng/dL.

Triiodothyronine (T3)
Triiodothyronine (T3) was measured in 2012-2013 in serum on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation) using a competition immunoassay method (Roche Diagnostics, Indianapolis, IN 46250). Bound T3 is released from the binding proteins in the sample by 8-anilino-1-naphthalene sulfonic acid (ANS). The laboratory CVs were 7.2% at a concentration of 121 ng/dL and 5.4% at a concentration of 354 ng/dL.

Thyroid Peroxidase, antibody (anti-TPO)
Thyroid peroxidase antibody (anti-TPO) was measured in 2012-2013 in serum on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation) using a competition immunoassay method (Roche Diagnostics, Indianapolis, IN 46250). The laboratory CVs were 6.0% at a concentration of 146 IU/mL and 10.2% at a concentration of 33 IU/mL.

Subclinical thyroid disease (hypo- and hyperthyroidism):
Subclinical thyroid disease, hypothyroidism and hyperthyroidism are common clinical entities that encompass mild to severe degrees of thyroid dysfunction. The term subclinical denotes the presence of disease without obvious symptoms, which means the evolution of disease might be at an early stage. Subclinical hypothyroidism occurs when serum TSH concentrations are elevated but T4 and T3 concentrations are normal. Likewise, subclinical hyperthyroidism occurs when serum TSH concentrations are low or undetectable but T4 and T3 concentrations are normal.

Hypo- and hyperthyroidism:
Overt hypothyroidism can be diagnosed when TSH concentrations are elevated and free T4 and T3 are below their reference range. Likewise, overt hyperthyroidism can be diagnosed when TSH concentrations are low or undetectable and free T4 and T3 are above their reference range.

Treatment for hypo- and hyperthyroidism and known disease:
Medication data files from each ARIC visit will be used to evaluate the intake of thyroid medications for treated hypothyroidism (thyroid replacement medication) or treated hyperthyroidism (methimazole, propylthiouracil). Self-reported diagnosis of thyroid disease at ARIC visits 3 and 4 will be taken into account.

Autoimmune thyroiditis:
Diagnosis is made by detecting elevated anti-thyroid peroxidase antibodies in the serum. Roche provides a cutoff of 34 IU/ml (32.7 IU/ml = 95% confidence interval) for their instruments (Elecsys systems 1010/2010 modular analytics E170 cobas e 411 and cobas e 601 analyzing machines)(16).

Measures of renal function:
GFR will be estimated by the CKD-EPI equations using an IDMS-standardized creatinine assay (17). Secondary analyses will examine cystatin C and the combination of creatinine and cystatin C (18, 19). eGFR will be expressed continuously and in clinically-relevant categories (stage 5: <15, stage 4: 15-29, stage 3b: 30-44, stage 3a: 45-59, stage 2: 60-89, stage 1: ≥90 mL/min/1.73m^2). Renal function decline will be defined as annual decline based on the difference in eGFR values between the baseline visit and one of the follow-up visits.

Incident renal endpoints:
We will use the newly updated definitions of incident renal endpoints in the ARIC Study (Grams *et al*, manuscript in preparation). Specifically, we will evaluate incident CKD, incident kidney failure, incident ESRD, and incident AKI. Incident renal events are based on measures of kidney function (such as the presence of eGFR falling below 60 ml/min/1.73 m^2 at a follow-up visit (visit 4 and 5) and a >25% decline in eGFR), and/or on kidney disease-related hospitalizations, death records and linkage to the USRDS by continuous active surveillance. Detailed descriptions of the definitions of each of these renal events and – if applicable - the underlying ICD codes are given in the ARIC documentation for the identification of incident renal disease.

Exclusions:
Missing information on exposures, outcomes or covariates of interest and race other than white or black. For analyses of incident kidney outcomes, we will exclude participants with prevalent kidney disease. For analyses of the thyroid function measures across levels of kidney function, we will exclude participants with thyroxine medication intake or antithyroid drug intake (methimazole, propylthiouracil).

Stratification:
At the minimum we will conduct stratification by sex, age, obesity status and race.

Covariates:
We will make use of several covariates: age, sex, race, smoking, C-reactive protein (CRP), BMI, physical activity, medication (thyroxine, methimazole, propylthiouracil),

diabetes status, bp, serum triglycerides, serum cholesterol, CHD status, white blood cell count (WBC) and serum albumin.

Statistical analyses:
We will generate descriptive statistics to examine the distribution of thyroid hormone concentrations and disorders and other characteristics of study participants including age, gender and race across levels of kidney function at baseline (eg, t-test, ANOVA, chi-squared tests). The association among thyroid function measures as well as thyroid disorders and renal function measures at baseline will be assessed through univariate and multivariable adjusted linear and logistic regression analyses.
The association between thyroid hormones and thyroid disorders at baseline and incident renal endpoints or kidney function decline will be assessed using Cox proportional hazards or Poisson regression. Appropriate methods will be used for model building and comparison (for example, nested models and likelihood ratio test). We will conduct sensitivity analyses comparing definitions of incident renal events.

Limitations:
- serum creatinine measured only at three time points during the follow-up period
- As with all observational studies, we will not be able to eliminate the possibility of residual confounding

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 #1949, Validation of inter-visit kidney events, Morgan Grams
- MP #2143, Association of FGF-23 levels with risk and progression of CKD: the ARIC study

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 number2009.24 (PI: Selvin); also covariate data from AS 2009.16 (PI: Selvin))

___ 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.

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