ARIC Manuscript Proposal # 3214

PC Reviewed: 8/14/18    Status: _____    Priority: 2
SC Reviewed: _________    Status: _____    Priority: ____

1.a. Full Title: Periodontal status and changes in retinal microvasculature and carotid intima-media thickness: a 15-year prospective study.

b. Abbreviated Title: Periodontitis and vascular changes.

2. Writing Group:
   Writing group members:
   Adrien Boillot, Philippe Bouchard, Sébastien Czernichow, Steven Offenbacher, Kevin Moss, Jim Beck, Others?

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

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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).
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We invite ARIC investigator(s) to participate in this manuscript

3. Timeline: About five months for data analysis, five months for the manuscript draft.

4. Rationale:
Periodontitis is a chronic inflammatory disease of the supporting tissues of the tooth that can cause tooth loss. Periodontitis can also affect systemic health by increasing the patients’ risk for other diseases such as cardiovascular diseases.

Previous study in ARIC found a positive relationship between periodontitis and carotid intima-media thickness. [1] Also, improvement in periodontal status is associated with a decrease in carotid intima-media thickness (CIMT). [2]

In a previous cross-sectional study based on ARIC data, we also observed a significant association between severe periodontitis and larger retinal venular diameter. [3] However, to date, there is no reported follow-up data on the relationship between periodontitis and changes in the retinal microcirculation lesions.

Finally, narrower retinal arterioles are associated with an increased carotid intima-media thickness. [4] Also, among hypertensive patients, narrower retinal arterioles and wider retinal venules are associated with increased CIMT. [5]

The scientific evidence linking periodontitis to other diseases is impeded by the lack of homogeneity in the clinical classifications of periodontal diseases. A robust risk assessment system based on periodontal and tooth profile definition, the Periodontal Profile Classes (PPC) has been recently validated with a companion periodontal index, the Tooth Profile Classes (TPC). This system, using latent class analysis (LCA), improves our ability to predict tooth loss and incident periodontal disease, as compared to previous disease classifications. [6] The study population (n=6,783) was extracted from the Dental Atherosclerosis Risk in Community Study (DARIC).

It is thus of interest to investigate the association between longitudinal changes in retinal microvasculature and periodontal diseases by using PPC and TPC classifications in the ARIC cohort. Also, it is interesting to assess the combine effect of periodontal status and retinal vascular changes on CIMT changes.

5. Main Hypothesis/Study Questions:

The present research proposal aims to explore, in a 15-year follow-up study, (1) the association between Periodontal Profile Classes (PPC) [6] plus the Tooth Profile Classes (TPC) [6] and changes in retinal microcirculation; (2) the association between Periodontal Profile Classes (PPC) [6] plus the Tooth Profile Classes (TPC) [6] and changes in carotid intima-media thickness; and (3) the association between changes in retinal microvasculature among different classes of periodontal status (using Periodontal Profile Classes (PPC) [6] plus the Tooth Profile Classes (TPC)) and changes in carotid intima-media thickness.

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).

Our analysis uses PPC and TPC as exposures. Changes in retinal arteriolar and venular calibers, and in CIMT are the outcomes. We plan to use age, ethnicity/center, sex, hypertension, lipids,
smoking and alcohol consumption, BMI, education, income, and number of missing teeth as control variables. ARIC Visit 4 (1996-1998) is the baseline and ARIC Visit 5 (2011-2013) is the endpoint.

Periodontal records are collected at baseline (Visit 4). Retinal photographs were taken at Visit 4 and 15 years after during Visit 5 to measure retinal arteriolar (CRAE) and venular (CRVE) calibers. CIMT was measured at Visit 4, and 15 years after during Visit 5.

The dental team has currently access to the periodontal status at baseline (Visit 4). All the other data of interest collected during Visits 4 and 5 will be requested once the research proposal will be approved. The dental team will be responsible for the analysis.

**Study question No1:** Changes in retinal arteriolar and venular calibers between Visits 4 and 5 (Δ CRAE and Δ CRVE) will be categorized into quartiles. Multinomial logistic regression models will be used to investigate the association between changes in retinal arteriolar and venular diameters between visits 4 and 5 and the presence of periodontitis at visit 4, after adjustment for control variables, summarized using propensity score. We plan to use propensity score because of the large number of confounders regarding the sample size and the inherent risk of overadjustment.

**Study question No2:** Change in carotid IMT between Visits 4 and 5 (Δ carotid IMT) was regressed using multivariable linear regression models across PPC/TPC classes and across quartiles of changes in retinal arteriolar and venular diameters between visits 4 and 5 (Δ CRAE and Δ CRVE categorized into quartiles), after adjustment for control variables summarized using propensity score.

**Study question No3:** Interaction between PPC/TPC classes and changes in retinal arteriolar and venular diameters will be tested. If an interaction exists, subgroup analyses will be conducted, based on periodontal status and changes in retinal arteriolar and venular diameters (no periodontitis and each quartile for changes in retinal arteriolar and venular diameters and periodontitis and each quartile for changes in retinal arteriolar and venular diameters, resulting in 8 levels of periodontal and retinal status).

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes  ____ 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? __X__ 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)?

There are many manuscript proposals that use dental variables as an exposure including but not limited to #492, 687, 861, 730, 827, 858, 913, 915, 929, 995, 1112, 1284, 1892, 2053 and 1859.

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* ___ 1996.01___)  
___    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 ____
REFERENCES


