ARIC Manuscript Proposal #2449

PC Reviewed: 10/14/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Associations between periodontal diseases and retinal microcirculation: a cohort study of risk in community-dwelling adults.

b. Abbreviated Title (Length 26 characters): Periodontitis and eye vessels

2. Writing Group:

Writing group members:

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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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3. Timeline: Statistical analysis: 4 months. Redaction of the manuscript: 2 months.

4. Rationale:

Previous studies in Dental ARIC found a positive relationship between periodontal pathogens and both coronary heart diseases (Beck, Eke et al. 2005) and carotid artery intima-media wall thickness (Beck, Elter et al. 2001). Host-parasite reactions induce a non-specific innate response that includes increases in serum CRP (Slade) and sICAM (Beck and Offenbacher). Consequently, periodontal diseases may have an impact on retinal vessel morphology. Several studies have found that retinal microvascular alterations are predictive factors for cardiovascular events (Klein, Klein et al. 2006; Wong, Islam et al. 2006; McGeechan, Liew et al. 2009). It is our overall hypothesis that periodontal diseases may be linked to retinal microcirculation, perhaps via the innate inflammatory response triggered by periodontal infections. Today, there is no publication exploring the association between periodontal diseases and microcirculation. Thus, it is of interest to investigate this relationship.

5. Main Hypothesis/Study Questions:

We hypothesize that inflammation due to periodontal diseases is associated with retinal microcirculation modifications. The aim of this study is (1) to explore the relationship between the clinical parameters of periodontal diseases and the retinal arteriolar and venular measures; and (2) to investigate the association between serum IgG antibodies against 17 periodontopathogens as a marker of systemic exposure to oral organisms, and retinal microcirculation parameters and (3) to determine whether serum markers of inflammation including serum CRP, IL-6 and sICAM are intermediary explanatory variables in the association between periodontal disease and retinal vascular pathology.

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: this cohort study of risk aims to compare changes in retinal vessel parameters recorded between ARIC visit 3 and ARIC visit 4 with subjects having moderate/severe periodontal disease or no/mild periodontal disease recorded at visit 4.

Inclusion: participants with both retinal vascular and periodontal measurements. One case (periodontal disease) will be frequency-matched to two controls by age, gender, ethnicity and community.

Exclusion: individuals not present at visit 4, subject with no retinal photograph or with ungradeable photographs, lack of data on diabetes mellitus status, body mass index, smoking and carotid and/or intima media thickness, subjects with less than 6 remaining teeth.

Outcome: The main outcome will be the difference in central retinal arteriolar and venular diameters between visit 3 and visit 4 (ΔCRAE, ΔCRVE).

Other variables of interest with specific reference to the time of their collection:

Clinical periodontal variables: periodontal status will be defined by extent of attachment loss ≥3 mm measured at visit 4: none/mild periodontitis (<10%), moderate periodontitis (10% to <30%) and severe periodontitis (≥30%). (Beck, Elter et al. 2001) (Elter, Champagne et al. 2004)

Biological periodontal variables: IgG antibodies against 17 periodontal organisms (Visit 4) will be analyzed as a categorical variable (tertiles). We will also examine serum levels of CRP, IL-6 and sICAM using tertiles.

Covariates: Covariates will include age (Visit 4), gender (Visit 4), race (Visit 4), carotid artery IMT (Visit 4), diabetes (Visit 4), LDL cholesterol (Visit 4), HDL cholesterol (Visit 4), triglycerides (Visit 4), hypertension (Visit 4), smoking (Visit 4), BMI (Visit 4), education (Visit 4), and race/study center (Visit 4).

Summary of data analysis: Characteristics at visit 4 will be described for subjects having moderate/severe periodontal disease and no/mild periodontal disease. We will initially use Chi-2 test to compare categorical variables (e.g., smoking) and t-test for continuous variables (e.g., retinal calibres). Additionally, t-test will be used to compare differences in retinal arteriolar and venular diameters between visit 3 and visit 4 for both groups. Multivariate linear models will be used to investigate the relationship between differences in retinal parameters (dependent variable. ΔCRAE, ΔCRVE) and clinical periodontal status assessment, biological periodontal variables (IgG antibodies against 17 periodontal pathogens) and covariates. For both ΔCRAE and ΔCRVE variables, four models will be calculated: Model A will be unadjusted, Model B will be adjusted for clinical periodontal status, biological periodontal variables (IgG antibodies against periodontal pathogens) and the interaction variable between periodontal status and total IgG antibodies against periodontal pathogens to adjust for individual differences in antibody response against

periodontal pathogens, model C will be additionally adjusted for socio-demographic and lifestyle factors (center, age, race, socioeconomic status, BMI, smoking), and model D for all covariates. Separate analysis will be conducted for all participants and for participants with no cardiovascular event at Visit 3. Moreover, a previous study conducted in ARIC found women with wider retinal venular diameter and narrower retinal arteriolar diameter had a higher risk of incident CHD.(McGeechan, Liew et al. 2008) As a consequence, multivariate logistic regression models will be used to investigate the relationship between at-risk retinal microcirculation status for CHD (yes/no) and clinical periodontal status assessment, biological periodontal variables (IgG antibodies against 17 periodontal pathogens) and covariates. The same four step approach will be used. A 2-sided P value of less than 0.05 will be regarded as significant in all analyses. For database management and statistical analysis, we will use SAS and R softwares.

If associations exist between serum markers and outcomes we will use the general approach described for antibody IgG levels described above. To assess the potential influence of serum inflammatory markers as intermediate explanatory variables, separate logistic models will be developed with or without the serum inflammatory marker to determine whether the variable impacts the contribution of periodontal disease.

Methodological limitations: The main limitation is the lack of periodontal data at visit 3 that preclude any attempt to evaluate the progression of periodontal disease over time.

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 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"? __ 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)?

Beck JD, Elter JR, Heiss G, Couper D, Mauriello SM, Offenbacher S. Relationship of periodontal disease to carotid artery intima-media wall thickness. Arterioscler Throm Vasc Biol 2001;21:1816-22.

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.

REFERENCES

Beck, J. D., P. Eke, et al. (2005). "Periodontal disease and coronary heart disease: a reappraisal of the exposure." Circulation **112**(1): 19-24.

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Elter, J. R., C. M. Champagne, et al. (2004). "Relationship of periodontal disease and tooth loss to prevalence of coronary heart disease." J Periodontol **75**(6): 782-790.

Klein, R., B. E. Klein, et al. (2006). "Are inflammatory factors related to retinal vessel caliber? The Beaver Dam Eye Study." Arch Ophthalmol **124**(1): 87-94.

McGeechan, K., G. Liew, et al. (2009). "Prediction of incident stroke events based on retinal vessel caliber: a systematic review and individual-participant meta-analysis." Am J Epidemiol **170**(11): 1323-1332.
McGeechan, K., G. Liew, et al. (2008). "Risk prediction of coronary heart disease based on retinal vascular caliber (from the Atherosclerosis Risk In Communities [ARIC] Study)." Am J Cardiol **102**(1): 58-63.
Wong, T. Y., F. M. Islam, et al. (2006). "Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA)." Invest Ophthalmol Vis Sci **47**(6): 2341-2350.