

ARIC Manuscript Proposal # 1443

PC Reviewed: 11/11/08
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1. a. Full Title:

The association between gingivitis and the local inflammatory mediators GCF-IL1b or PGE2 on the increased level of serum IL-6, C-reactive protein, or white blood counts among non-Hispanic White and Black population

b. Abbreviated Title (Length 26 characters):

Local and systemic inflammation

2. Writing Group: Writing group members:

- O. Mireille Andriankaja - Kevin Moss - James Beck
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. MOA [please confirm with your initials electronically or in writing]

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3. Timeline: November 2008 – manuscript approval
January 2009 – complete data analysis

March 2009 - complete draft for approval by working group

April 2009 – submit manuscript to Publications Committee

4. Rationale:

Periodontal disease has two general subcategories: gingivitis and periodontitis. Gingivitis is an inflammatory condition that represents the more prevalent and milder form of the disease and is characterized by redness, swelling and bleeding of tissues. Generally, gingivitis does not result in destruction of the periodontal ligament or supportive bone. Gingival inflammatory conditions may be chronic or may present as acute episodes, either restricted to a small area of the mouth or generalized in the oral cavity. Periodontitis, on the other hand, is the more serious and destructive form of the disease. When a person is diagnosed with periodontitis, practitioners tend to treat periodontitis while overlooking the extent of gingivitis that might also be present in the oral cavity. Consequently, there is an inflammatory burden associated with chronic, generalized gingivitis that has been largely ignored (except for toothpaste companies).

Chronic gingivitis and local inflammatory mediators, such as IL-1b and PGE2, may be associated with increased levels of systemic inflammatory mediators, such as IL-6, C-reactive protein (CRP), and white blood counts (WBC), all known to be risk factors for cardiovascular disease (1,2). However, this local and systemic inflammatory connection has not been demonstrated in a large community database. In addition, no conclusive evaluation of this association across different races/ethnicities has been done. However, in order to develop effective therapeutic regimens and preventive controls, particularly in view of the association between periodontitis/gingivitis and CVD in a given population, we must determine 1) whether local inflammation increases the levels of systemic inflammatory mediators and, once such association is established 2) whether it is different across different races/ethnicities.

5. Main Hypothesis/Study Questions:

Does the presence of chronic gingivitis or the production of local inflammatory mediators, such as IL-1b and PGE2, increase the levels of systemic inflammatory mediators, such as IL-6, CRP, and white blood counts? If so, is the association the same across races/ethnicities?

Hypotheses:

- 1) Chronic gingivitis or local inflammatory mediators, such as IL-1b and PGE2, are associated with increased levels of systemic inflammatory mediators, such as IL-6, CRP, or white blood counts.
- 2) The association is different between non-Hispanic White and Black population.

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: Cross-sectional

Inclusion criteria: Have only healthy gingiva or gingivitis

Exclusion criteria: - Edentulous

- Participants with contraindications on periodontal probing
- Participants with periodontal disease (any pocket depth > 3mm)
- Participants with chronic systemic inflammatory conditions
- Participants without information on race/ethnicity and without information on inflammatory mediators (GCF -IL-1b, GCF - PGE2, serum IL-6; CRP, and WBC)

Dependent variables: Serum levels of IL-6, CRP or WBC (categorized as high/low)

Independent variables:

1) Gingival status

Case definition: - Healthy gingiva: having pocket depth (PD) \leq 3mm and a total number of tooth sites with bleeding on probing (BOP) <10%
- Gingivitis: having PD \leq 3mm and a total number of tooth sites with BOP \geq 10%

2) Local inflammatory mediators: GCF level of IL-1b; GCF level of PGE2

Covariates: age; gender; race/ethnicity; diabetes status; educational levels; plaque index scores; tooth loss, hypertension; BMI; waist-hip ratio; triglycerides, total cholesterol, HDL-C, and LDL-C

Data analysis: - Descriptive characteristics of the study population

- Bivariate analysis of the association between gingivitis status/GCF- IL-1b or GCF- PGE2 and high/low (median as cutoff point) levels of serum IL-6, CRP or WBC
- Bivariate analysis of the association between gingivitis/GCF- IL-1b or GCF- PGE2 and serum IL-6, CRP or WBC by race/ethnicity
- Study of potential correlations between all variables; potential interaction between gingivitis /IL-1b/PGE2 and race/ethnicity on the association with serum IL-6, CRP or WBC; potential interaction between relevant variables (age, gender) and the independent variables
- Multivariate analysis of the association between gingivitis/GCF-IL-1b/GCF-PGE2 and systemic levels (high/low) of serum IL-6, CRP or WBC, using logistic regression with effect modification terms (may need separate models by race/ethnicity if there is an interaction)

Limitation: cross-sectional study with temporal sequence issue. No causal inference

7. a. Will the data be used for non-CVD analysis in this manuscript? ☒ Yes ☐ No

b. If Yes, is the author aware that the file ICTDER02 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

(The file ICTDER02 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 ☒ No

8. b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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 publication lists under the Study Members Area of the web site at: <http://www.cscce.unc.edu/ARIC/search.php>.

☒ 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)?

The most related manuscript proposal in ARIC is our previous study (OM Andriankaja et al.) with manuscript # 1303. Previous published articles using the ARIC data have looked at the association between periodontal disease and various outcomes (3, 4), while our work is only restricted to participants with biofilm-gingival interface (BGI) gingivitis and various outcomes. Our previous proposal assessed the potential association between local or systemic inflammatory mediators and the presence of BGI-gingivitis in participants with or without type 2 diabetes. However, the present proposal examines the potential association between BGI-gingivitis or local inflammatory mediators and increased levels of systemic inflammatory mediators.

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

11. b. If yes, is the proposal

☒ 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.cscce.unc.edu/aric/forms/>

References:

1) Berliner JA, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, Watson AD, Lusis AJ. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. *Circulation*. 1995;91:2488-2496.

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- 2) Arima H, Kubo M, Yonemoto K, Doi Y, Ninomiya T, Tanizaki Y, Hata J, Matsumura K, Iida M, Kiyohara Y. High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama study. *Arterioscler Thromb Vasc Biol.* 2008 Jul;28(7):1385-91.
- 3) Beck JD, Offenbacher S. Relationships among clinical measures of periodontal disease and their associations with systemic markers. *Ann Periodontol.* 2002 Dec;7(1):79-89.
- 4) Slade GD, Ghezzi EM, Heiss G, Beck JD, Riche E, Offenbacher S. Relationship between periodontal disease and C-reactive protein among adults in the Atherosclerosis Risk in Communities study. *Arch Intern Med.* 2003 May 26;163(10):1172-9.