ARIC Manuscript Proposal # 827

PC Reviewed: 09/18/01   Status: __A_   Priority: ___1_
SC Reviewed: 09/18/01   Status: __A_   Priority: ___1_

1.a.   Full Title: Relationship between Periodontitis and Stroke/Transient Ischemic Attack: The ARIC Study

  b. Abbreviated Title (Length 26 characters): Periodontitis and Stroke/TIA

2.   Writing Group (list individual with lead responsibility first):

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3.   Timeline: Obtain data set: September 2001
                  Begin statistical analysis: September 2001
                  Complete statistical analysis: November 2001
                  Complete manuscript: March 2002

4.   Rationale: A number of cross-sectional (1, 2), case-control (3-6), and longitudinal reports (7-11) have suggested that the chronic infection inherent in periodontitis are related to cardiovascular events, however, three longitudinal studies did not support such an association (12-14). The results of studies that specifically examined the relationship between clinical periodontitis and stroke have all been positive (3, 7, 15, 16).

       A mechanism has been proposed whereby the chronic bacterial infection of periodontitis creates a burden of bacterial pathogens, bacterial antigens, endotoxins and inflammatory cytokines that contribute to and modify the process of atherogenesis and thromboembolic events (17). In response to infection and inflammation, certain persons may exhibit greater expression of a profile of local gingival crevicular fluid and systemic serum mediators of the inflammatory response, and may be at increased risk for atherosclerosis due to the effects of these circulating inflammatory products on the atherosclerotic process. These plaques may result in decreased vascular patency and/or decreased compliance of the vessel wall. Ultimately, plaques may rupture, resulting in full or partial occlusion of the vessel lumen distal to the plaque, precipitating an ischemic stroke.

We propose a cross-sectional study of data obtained from the Dental ARIC cohort at Visit 4. Prevalence of reported or detected stroke/transient ischemic attack (TIA) through visit 4 will be compared for persons with and without periodontal disease. Prevalent stroke cases will be supplemented with incident strokes through 1998. In addition, a case control study of stroke/TIA with validation using MRI will be conducted.

References:

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17. Beck JD, Offenbacher S, Williams R, Gibbs P, Garcia R. Periodontitis: a risk factor for coronary heart disease? Ann Periodontol 1998;3(1):127-41.

5. Main Hypothesis/Study Questions:

1) Persons with reported or detected stroke/TIA (cases) through visit 4 will be more likely to have clinically measured periodontitis at visit 4, compared to persons with no history of stroke/TIA.

2) Cases with history of stroke/TIA <u>and</u> periodontitis will be more likely to exhibit high levels of gingival crevicular fluid IL-1β and serum CRP, IL-6, and TNF$_\alpha$, compared to cases without periodontitis.

3) Prevalence of reported or detected stroke/TIA will be positively and monotonically associated with the extent and severity of periodontal disease (after adjustment for attributes presumed to be risk factors for both conditions).

6. Data (variables, time window, source, inclusions/exclusions):

Outcome variables: Reported or detected stroke/TIA through ARIC visit 4, incident stroke cases from ARIC surveillance through 1998 (mainly for validation of reported or detected stroke/TIA and for assessment of event-specific associations), and MRI cases for cerebral infarcts (to look at in case control associations with periodontal disease).

Main independent variable: The main independent variable is periodontal disease, defined by "extent of periodontal attachment loss (AL) at least 3 millimeters". Periodontal case status will be defined as: No periodontitis = extent AL < 3%, mild periodontitis = extent AL 3% - < 30%, and severe periodontitis = extent AL 30%+. Quintiles of extent AL will be used to evaluate a positive monotonic relationship between periodontal disease and stroke/TIA.

Covariates. Sex, age in years at visit 4, race and ARIC field center, 3 levels of education (to control for SES), hypertension (definition 5), smoking (current heavy, current light, former heavy, former light, or never), diabetes mellitus (definition 2), plasma LDL, HDL, and triglyceride levels, body mass index, gingival crevicular fluid IL-1β and serum CRP, IL-6, TNFα. In addition, a subset of ARIC subjects consisting of 207 periodontal disease cases and 200 controls have had an expanded set of analytes processed. These include: coagulation and fibrinolytic activity F 1+2 (D-dimer), endothelial TM, Fibrinogen, fibrinolytic plasminigen Tpa PAI-1, inflammatory CRP (in progress), platelet beta TG, VWF (Von Willebrand's Factor), E-selectin (in progress), IL-6 (in progress), IL-6 receptor (on hold), TNF alpha (in progress), TNF alpha receptor (on hold).

Time window. This study will be a cross-sectional study of the data obtained from ARIC cohort members at Visit 4, the 1996-98 examination cycle.

Inclusions/exclusions. This study will include Dental ARIC cohort members for whom periodontal measures and reported or detected stroke/TIA were available. Persons who were not African-American or White will be excluded. 6,796 men and women had periodontal examinations at Visit 4.

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 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?   __X_ Yes   ____ No
    (This 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   __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 ICTDER02 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

    ___X__ Yes   _____ No