1. a. Full Title:

The influence of type 2 diabetes on the host inflammatory response associated with gingival inflammation

b. Abbreviated Title (Length 26 characters):

Type 2 diabetes and gingivitis

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. __MOA___ [please confirm with your initials electronically or in writing]

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3. Timeline: October 2007 – Manuscript Approval
November 2007 – complete data analysis
December 2007 - complete draft for approval by working group
January 2008 – Submit manuscript to Publications Committee
4. **Rationale:**

Periodontal disease has two general sub-categories, gingivitis and periodontitis. Gingivitis is an inflammatory condition that represents the more prevalent, mild form of the disease where there is redness, swelling and bleeding of tissues. Gingivitis, generally, does not have destruction of the periodontal ligament and support bone, and it may be restricted to a small area in the mouth or be generalized and may come and go or be chronic. Periodontitis is the more serious, destructive form of the disease. When a person is diagnosed with periodontitis, tend to ignore the extent of gingivitis that may also be in the mouth and concentrate on the periodontitis. However, there is an inflammatory burden associated with chronic, generalized gingivitis that has been largely ignored (except for toothpaste companies).

Diabetes is a well-known risk factor for periodontal disease. Individuals with type 2 diabetes may have over-expression of inflammatory response to bacterial pathogens leading to chronic gingival inflammation. Proinflammatory mediators such as IL-1β, IL-6, C-reactive protein (CRP) and prostaglandin E2 (PGE2) are all known to be responsible for periodontal tissue destruction (1, 2). These mediators have been found to be high in gingival crevicular fluid of individuals with periodontitis, but this relationship has not been investigated for gingivitis (2, 3). A significant proportion of diabetic individuals may be exposed to chronic gingivitis, which may persist in the mouth unnoticed by the individual. Unfortunately, very few studies have assessed the particular link between type 2 diabetes and gingivitis as they have only examined the association between diabetes and periodontitis, ignoring gingivitis.

5. **Main Hypothesis/Study Questions:**

Type 2 diabetic study participants have higher local and systemic proinflammatory mediator levels, which may lead to a higher prevalence of chronic gingivitis as compared to non-diabetic participants.

**Hypotheses:** The levels of local and systemic proinflammatory mediators, such as GCF-IL-1β, GCF-PGE2, and serum IL-6 and CRP are positively associated with gingivitis prevalence in all study participants, with effect modification being present by diabetic status.

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:**
- Non-smokers
- Have only healthy gingiva or gingivitis

**Exclusion criteria:**
- Edentulous
- Participants with contraindications for periodontal probing
- Participants with periodontal disease (any pocket depth > 3mm)
- Participants with chronic systemic inflammatory conditions
- Participants without information on diabetic status, and inflammatory mediators (GCF levels of IL-1β, GCF levels of PGE2, serum IL-6 and CRP)
Dependent variable: gingivitis status (yes, no)

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

Independent variables: diabetes status (effect modification and stratification); GCF IL-1b, GCF PGE2, serum IL-6 and CRP

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

Data analysis: 
- Descriptive characteristics of the study population
- Bivariate analysis of the association between each variable and gingivitis status
- Bivariate analysis of the association between GCF- IL-1b, GCF- PGE2, serum IL-6, CRP and gingivitis status by diabetic status
- Multivariate analysis of the association between inflammatory mediators and chronic gingivitis using logistic regression with effect modification term (may need separate models for each mediator by diabetic status)

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? __X__ 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? ___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”? _____ 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)?
The most related manuscript proposal in ARIC is the study of Dr. Janet Southerland and the colleagues (manuscript # 730). Their study assesses the potential interactions between periodontal disease, diabetes, and CVD outcomes such as intima-media thickness (IMT), and plaque shadowing.
However, our manuscript proposal examines the potential interaction between diabetes, host inflammatory response, and gingivitis.

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/

References: