1. a. **Full Title:** Periodontal Disease and the Risk of Type 2 Diabetes  
   b. **Abbreviated Title (Length 26 characters):** Periodontitis & Diabetes

2. **Writing Group:**  
   Indra Mustapha, Elizabeth Selvin, Fred Brancati, Steven Offenbacher,  
   Jim Beck

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

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3. **Timeline:**

   Obtain data set: Jan 2012  
   Begin statistical analysis: January 2012  
   Complete statistical analysis: March 2012  
   Complete manuscript: May 2012

4. **Rationale:**
**Periodontal disease definition**  Periodontal disease is defined as loss of attachment of the periodontium, whereby gingival epithelial cells and connective tissue attachment, and bone around the tooth migrate apically (downwards) away from the cemento-enamel junction. This loss of periodontal tissue is caused by the host response to mostly gram-negative bacteria and their toxins found in plaque. It is quite common in the U.S. adult population and is often seen clinically and radiographically after the age of 35 years old with its prevalence (65-78%) and severity (16-46%) increasing in the elderly and African American populations. (Beck et al., 1990)

**Figure 1: Periodontium: Healthy vs. Disease**

![Periodontium Healthy vs Disease](image)

**Periodontal disease provokes systemic inflammation.**  Acute endoxemia, by injection of E. coli lipopolysaccaride (LPS) has been shown to induce insulin resistance in cell receptors in adipose cells (Mehta et al., 2010). In periodontal; disease, LPS endotoxin is expressed on cell walls of periodontal pathogens such as *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*. These endotoxins act via TLR 4 to trigger inflammation and loss of periodontal attachment around teeth. While both pathogens may be present in active periodontitis, *Porphyromonas gingivalis* is commonly associated with a chronic slowly progressive generalized form of periodontal disease and *Actinobacillus actinomycetemcomitans* is more commonly associated with an aggressive form of periodontitis, which can present clinically in younger ages. Antibodies are produced to these periodontal pathogens. These serum antibody titers are the most specific markers to reflect systemic exposure to periodontal pathogens. Inflammatory mediators, such as Prostaglandin E2, have also been measured in gingival crevicular fluid (GCF) collected from the gingival crevice to assess periodontal disease. (Andriankaja, 2009)
Both diabetes and periodontal disease have been found to result in an elevation of inflammatory cytokines as a host response. Gram-negative bacteria found in periodontal disease have been found to result in elevated levels of these cytokines, such as Prostaglandin E2 (PGE2) in both the gingival crevicular fluid and in peripheral blood in diabetics with periodontal disease. Diabetics with advanced periodontal disease had two-fold higher levels of PGE2 and Interleukin-1β (IL-1β) when compared to diabetics with milder forms of periodontal disease (Salvi, et al., 1998) Similarly, tumor necrosis factor α (TNF-α), another cytokine commonly associated with periodontitis, was found to exacerbate insulin resistance (Nishamura et al. 2003). Salvi et al. however, found only marginal elevations of TNF-α in diabetics with periodontal disease when compared to non-diabetics with periodontal disease. Interleukin-1β (IL-1β) is expressed in both periodontal disease and in diabetics and is believed to play a role in the pathogenesis in both diseases. Kurtis et al. showed that gingival crevicular levels of IL-1β were highest in diabetics (2.43 +/- 0.97 ng/ml, followed by those with periodontitis (1.31 +/- 0.92 ng/ml) and these elevations were significantly higher than their healthy controls (0.62 +/- 0.58 ng/ml, p<0.05) Protein kinase C, produced by neutrophils in response to periodontal disease was found to be highly correlated with glycosylated hemoglobin levels (r=0.71 p<0.001). (Karima et al., 2005) Thus, the hypothesis of a bidirectional relationship between periodontal disease and diabetes may be due to the inflammatory response to periodontal disease as measured by specific serum markers.

**A variety of systemic inflammatory markers predict the subsequent occurrence of type 2 diabetes.** Markers for inflammation, such as high white blood cell count, predict the onset of diabetes with an odds ratio of 1.9 (95% CI: 1.6-2.3) in a 7 year longitudinal study of the ARIC cohort. (Schmidt, MI, et al.1999). C-reactive protein (CRP), an acute phase response protein, was elevated in a cross-sectional study of subjects with diabetes (Saito, T, 2003). However, CRP has been found to be elevated for reasons other than diabetes, such as advanced periodontal disease, obesity, stroke, myocardial infarcts or other infections and is not specific to exposure to diabetes. Serum interleukin-6 (IL-6), another measure of systemic inflammation is elevated in patients with diabetes (Andriankaja et al., 2009).

**Insulin resistance at the cellular level appears to mediate the relationship between systemic inflammatory markers and type 2 diabetes.** Inflammatory cytokines are known to activate cell signaling phosphorylation cascades such as MAP-kinase and NFkB pathways. (Evans, 2002) These pathways have multiple effects on cellular activities to include insulin resistance, insulin secretion and further cytokine production. (Figure 2), and has been found to be a significant negative modifier to antibodies to oral pathogens. (Singer, RE, 2009) An animal model inducing periodontal disease in lean rats found an elevation of fasting glucose (p=0.003), insulin, (p=0.008) and insulin resistance (p<0.001). (Pontes AC, 2007) This animal study has been the first to look at the progression to a pre-diabetic state that can be attributed to periodontal inflammation as an independent risk factor.
Identifying modifiable sources of inflammation might lead to novel approaches to prevent type 2 diabetes. Studies aimed at assessing the effect of treatment of periodontal disease on metabolic control of diabetes have yielded conflicting results. One study found a 10% reduction in glycosylated hemoglobin values with non-surgical periodontal and antibiotic therapies in diabetic subjects. (Grossi et al., 1996) Other studies have found similar outcomes with similar treatments (Miller et al., 1996, Grossi et al., 1996). A meta-analysis published December 2005, found that the overall reduction in glycosylated hemoglobin in subjects with diabetes mellitus after non-surgical periodontal therapy was 0.57% for four studies and this reduction was not statistically significant (p=0.82) (Janket, 2005). These trials all used clinical assessment to determine successful periodontal therapy in diabetics compared to normoglycemics. The non-significant effect of periodontal therapy on glycosylated hemoglobin does not mean that periodontal therapy as no effect on this pathway since glycosylated hemoglobin is not sensitive to immediate or short-term effects on insulin resistance. The drug thiazolidinione, used to improve insulin sensitivity, has been shown to inhibit LPS Porphyromonas gingivalis induced cytokine production in adipocytes in vitro. (Yamaguchi M, 2005). Porphyromonas gingivalis is not completely eradicated even after successful periodontal therapy. It is biologically plausible that the most sensitive assessment of exposure to periodontal inflammation involves periodontal pathogens and measures of their systemic levels, such as Porphyromonas gingivalis serum antibodies.

Periodontal disease has been proposed as one source of inflammation that might predispose adults to developing diabetes. Though the hypothesis of a bidirectional pathway between periodontal disease and diabetes has been proposed, few studies have addressed periodontal disease before the occurrence of diabetes (Taylor, 2001). Periodontal disease has also been shown to increase the risk of other systemic conditions such as cardiovascular disease in adults and poor pregnancy outcomes. (Humphrey, 2008, Offenbacher, 2006). Localized periodontal inflammation is now known to have systemic effects on general health. Compromised oral health may increase the risk of a pre-diabetic status mediated through diet and systemic inflammation. This pre-diabetes is known risk factor future diabetes. There are no known published longitudinal clinical reports of exposure to periodontitis and the subsequent risk of diabetes.

ARIC Database

Because of the prior work of Drs. Beck and Offenbacher at UNC, the ARIC database contains ample data to characterize periodontal disease in ARIC participants at visit 4. These data include antibody levels to the periodontal pathogens Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans, gingival crevicular fluid levels of IL-1β (GCF- IL-1β), gingival crevicular fluid levels of prostaglandin (PG-E2), and clinical periodontal status.
5. **Main Hypothesis/Study Questions**:

Our central hypothesis is that periodontal disease leads to systemic inflammation and thereby to insulin resistance and future type 2 diabetes. To test our hypothesis, we propose to conduct two related analyses—one cross-sectional, one longitudinal.

**Specific Aim 1**
Hypothesis:

Periodontal disease, characterized by high serum IgG titers to oral pathogens, oral markers of inflammation, and evidence of periodontal disease on clinical examination, is cross-sectionally associated with impaired glucose tolerance (IGT), and elevated fasting glucose (FG).

Description of Database:

Dental ARIC, an ancillary study funded by the National Institute of Dental and Craniofacial Research (NIDCR), was conducted during ARIC visit 4 in 1996 through 1998 and is cross-sectional in design. The Dental ARIC consisted of an oral examination, collection of serum, and interviews. Of those ARIC cohort members examined at baseline, responders to a screening interview were selected. Respondents with no teeth or a medical contraindication to probing were excluded, while some refused the dental exam. Participant missing serum samples further reduced the number with both dental examinations and antibody level assessments to 4585. Follow-up interviews occurred yearly to assess participants’ health status. Participants continued to receive ongoing telephone interviews to report changes in medical history.

Table 1: The ARIC STUDY: Interviews and Procedures by Examination

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Visit 4 1996-1998 (n)</th>
<th>Ongoing Follow up (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody levels to Porphyromonas gingivalis</td>
<td>4500</td>
<td>4500</td>
</tr>
<tr>
<td>Antibody levels to Actinobacillus actinomyctemcomitans</td>
<td>4500</td>
<td>4500</td>
</tr>
<tr>
<td>Clinical Periodontal Exam</td>
<td>4500</td>
<td>4500</td>
</tr>
<tr>
<td>Gingival crevicular levels of IL-1β</td>
<td>725</td>
<td>500</td>
</tr>
<tr>
<td>Gingival crevicular levels of PG-E2</td>
<td>725</td>
<td>500</td>
</tr>
</tbody>
</table>

Exposures:

1) Serum Markers of Prior Periodontal Disease Exposure:
2) Local Inflammatory Markers of Periodontal Disease:
   a) Gingival crevicular fluid levels of IL-1β (GCF-IL-1β).
   b) Gingival crevicular fluid levels of prostaglandin (PG-E2)
   The variable GCF-IL-1β will be measured as the level of gingival crevicular fluid units (ng/mL). Subjects will be considered to have elevated levels of GCF-IL-1β levels at ≥136.2 ng/mL. The variable PG-E2 will be measured as the level of gingival crevicular fluid units (ng/mL). Subjects will be considered to have elevated levels of PG-E2 levels at ≥277.2 ng/mL.

3) Clinical Assessments of Periodontal Inflammation:
   a) bleeding upon probing
   b) periodontal pockets (rounded down to the nearest mm)
   Using the two parameters above, subjects have been classified into 5 groups (Offenbacher, 2007)
   1) probing depth (PD) ≤3mm, bleeding upon probing ≤10%
   2) probing depth (PD) ≤3mm, bleeding upon probing ≥10%
   3) one or more sites with PD≥4mm, bleeding upon probing ≤10%
   4) one or more sites with PD≥4mm, bleeding upon probing <50%
   5) one or more sites with PD≥4mm, bleeding upon probing ≥50%

Inclusion Criteria/Exclusion Criteria
Subjects who were taking antibiotics for any condition, including for premedication prior to dental examinations for prevention of bacterial endocarditis or infection of orthopedic joint replacements will be excluded from the analysis. We mostly excluded endocarditis and joint group already. Subjects taking medication for diabetes or having a positive medical history for diabetes will also be excluded from the analysis.
<table>
<thead>
<tr>
<th>Table 2-Summary of variables to be included in Specific Aim 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim 1</td>
</tr>
<tr>
<td><strong>Primary endpoints</strong> (American Diabetes Association Classification)</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Main independent variables</strong></td>
</tr>
</tbody>
</table>
Data Analysis:

This data set consists of approximately 5000 subjects with serum antibody levels to periodontal pathogens and 725 subjects with measured gingival crevicular fluid levels of IL-1β (GCF-IL-1β), and PG-E2 obtained from visit 4. All subjects have periodontal dental assessments from visit 4, and blood sugar levels from visits 2, 3 and 4. Power calculations for the mean detectable differences are shown for impaired glucose tolerance as a dichotomous outcome. (Table 3), and for FG, 2 hour glucose and glycosylated hemoglobin assays as continuous outcomes (Table 4). Multivariable logistic regression models will be used to compare glucose levels in subjects with insulin resistance in nondiabetic subjects (primary dichotomous outcomes) and the Chi-squared tests for significance will be performed. Linear regression and t-tests for the continuous outcomes will be explored. These relationships and all statistical analyses will be conducted using Stata 9.1 (Stata, College Station, TX). Regression models will adjust for confounders such as age, sex, smoking, BMI, tooth loss, oxidative stress levels, race, prior history of cardiovascular events, and dietary mediators such as fats, high fiber, high glucose consumption and total caloric intake will be included. Assessment of interactions of periodontal disease exposure (antibody levels), cardiovascular disease, age, and BMI are planned (Table 2).
Table 3- Minimal Detectable Differences For Blood Glucose Levels (Primary Outcomes) at Different Power Levels In Planned Logistic Regression (Serum antibodies n=5000, alpha=0.05, \( p_1 \)=prevalence of people in the general population with diabetes= 5.0%, \( p_2 \)=hypothesized proportion of people with diabetes with high antibody levels=7.5%)

<table>
<thead>
<tr>
<th>Power</th>
<th>Minimal Detectable Difference-Odds Ratios (( \Delta ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>1.38</td>
</tr>
<tr>
<td>85%</td>
<td>1.42</td>
</tr>
<tr>
<td>90%</td>
<td>1.76</td>
</tr>
</tbody>
</table>

Table 4-Minimal Detectable Differences for Blood Glucose Levels at Different Power Levels in Planned Logistic Regression (Serum antibodies n=5 000, alpha=0.05, \( sd_1 \)=standard deviation of assays of population of without diabetes, \( sd_2 \)=hypothesized standard deviation in population with high antibody levels= \( sd_1 \), assuming equal variances)

<table>
<thead>
<tr>
<th>Power</th>
<th>Minimal Detectable Difference-Odds ratios (( \Delta ))</th>
<th>FG (mg/dl)</th>
<th>2hr Glucose (mg/dl)</th>
<th>A1-C (%)</th>
</tr>
</thead>
</table>


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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>1.14</td>
<td>3.73</td>
<td>0.16</td>
</tr>
<tr>
<td>85%</td>
<td>1.21</td>
<td>3.94</td>
<td>0.17</td>
</tr>
<tr>
<td>90%</td>
<td>1.32</td>
<td>4.38</td>
<td>0.18</td>
</tr>
</tbody>
</table>

\[ \text{sd}_1 = 20.5 \quad \text{sd}_1 = 66.7 \quad \text{sd}_1 = 1.18 \\
\text{sd}_2 = 20.5 \quad \text{sd}_2 = 66.7 \quad \text{sd}_2 = 1.18 \]

**Limitations**

We anticipated missing data for many of the variables used in the regression model. Reasons for missing data may not be assessed with this available data and assumption of this missingness (missing completely at random, missing at random, or not missing at random) must be correct for the chosen model to be appropriate. Imputation with statistical means (Hotdeck in Stata) may need to be considered. Since the local inflammatory assessments GCF-1β and PG-E2 databases are one third the size of the antibody assessment sample size, the antibody and periodontal assessment will be the primary analysis, and the analyses of GCF and PG-E2 databases will be used to confirm the primary analysis. The small sample sizes, may compromise the precision of the calculated estimates.

**Specific Aim 2**

**Hypothesis:**

Exposure to periodontal inflammation, (using serum IgG, local inflammatory markers, systemic inflammatory markers and clinical exam evidence), predicts the subsequent occurrence of incident type 2 diabetes.
Experimental Design:
Observational studies using ARIC (longitudinal subset) AFU database.

Description of Databases:

ARIC AFU – The Atherosclerosis Risk in Communities study was followed-up by telephone interviews yearly to assess participants’ health status in an AFU study. These participants self-reported changes in medical history. A nearly complete data set is expected (n= 5000).

Exposures:

1) Serum Markers of Prior Periodontal Disease Exposure:
   a) Serum IgG antibodies to Porphyromonas gingivalis
   b) Serum IgG antibodies to Actinobacillus actinomyctemcomitans
   This variable will be measured as the level of antibody response to the periodontal pathogen Porphyromonas gingivalis and Actinobacillus actinomyctemcomitans in Elisa units (EU). Subjects will be considered seropositive for P. gingivalis and A. actinomyctemcomitans when the corresponding IgG levels reach >/= +5.0 EU.

2) Local Inflammatory Markers of Periodontal Disease:
   a) Gingival crevicular fluid levels of IL-1β (GCF- IL-1β).
   b) Gingival crevicular fluid levels of prostaglandin (PG-E2)
   The variable GCF- IL-1β will be measured as the level of gingival crevicular fluid units (ng/mL). Subjects will be considered to have elevated levels of GCF- IL-1β levels at >/=136.2 ng/mL. The variable PG-E2 will be measured as the level of gingival crevicular fluid units (ng/mL). Subjects will be considered to have elevated levels of PG-E2 levels at >/=277.2 ng/mL.

3) Clinical Assessments of Periodontal Inflammation:
   a) bleeding upon probing (BOP)
   b) periodontal probing depth (PD)(measured to down to the nearest mm)

Using the two parameters above (BOP and PD), subjects have been classified into 5 groups (Offenbacher, 2007):

1) probing depth (PD) ≤3mm, bleeding upon probing ≤10%
2) probing depth (PD) ≤3mm, bleeding upon probing ≥10%
3) one or more sites with PD≥4mm, bleeding upon probing ≤10%
4) one or more sites with PD≥4mm, bleeding upon probing <50%
5) one or more sites with PD≥4mm, bleeding upon probing ≥50%

Inclusion Criteria/Exclusion Criteria:
Subjects who were taking antibiotics for any condition, including for premedication prior to dental examinations for prevention of bacterial endocarditis or infection of orthopedic joint replacements will be excluded from the analysis. Subjects who had type 2 diabetes at baseline will also be excluded from the analysis.

Table 5: Summary of variables to be used in Aim 2
<table>
<thead>
<tr>
<th><strong>Primary endpoint</strong></th>
<th><strong>Aim 2</strong></th>
<th><strong>Aim 2</strong></th>
<th><strong>Aim 2</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Categorical</strong></td>
<td>DM-yes/no</td>
<td>Continuous</td>
<td>AFU self-report (ongoing)</td>
</tr>
<tr>
<td><strong>Continuous</strong></td>
<td>FG</td>
<td>2-h glucose</td>
<td>HbA1c</td>
</tr>
<tr>
<td><strong>Main independent variables</strong></td>
<td>Continuous Antibody levels to periodontal pathogens-ELISA units GCF-1β PG-E2 Clinical periodontal status</td>
<td>Continuous Antibody levels to periodontal pathogens-ELISA units GCF-1β PG-E2 Clinical periodontal status</td>
<td>Visit 4</td>
</tr>
<tr>
<td><strong>Covariates</strong></td>
<td>Age, Sex, Cardiovascular disease, BMI, Fiber intake, Fat intake, Total caloric intake, Tooth loss</td>
<td>Age, Sex, Cardiovascular disease, BMI, Fiber intake, Fat intake, Total caloric intake, tooth loss</td>
<td>Visit 1</td>
</tr>
<tr>
<td><strong>Interactions/Effect Modifiers</strong></td>
<td>Age, Smoking, Cardiovascular disease, BMI, Oxidative stress</td>
<td>Age, Smoking, Cardiovascular disease, BMI, oxidative stress</td>
<td>Visit 1</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>Incidence rate ratio, person-yr approach, Kaplan-Meier, Cox-proportional Hazards</td>
<td>Linear Regression</td>
<td></td>
</tr>
</tbody>
</table>

DM=diabetes mellitus
IGT=impaired glucose tolerance
FG=fasting glucose
2-h glucose=two hour post-load glucose
A1-C=glycosylated hemoglobin
Gingival crevicular fluid-IL-β=GCF-1β
Prostaglandin-PG-E2

Data Analysis:

This longitudinal analysis will compare subjects without initial diabetes to those without diabetes but elevated antibody levels, local and systemic markers of inflammation, and clinical periodontal disease with the primary outcome of diabetes (yes/no) over time. This time to event data can be analyzed with Kaplan-Meier survival curves and Cox-proportional hazard model where time of diabetes is year of AFU report. Incidence rate ratios and person-year ratios can be calculated. The dependent variables of antibody level (low/high) to periodontal pathogens *P. gingivalis* and *A. actinomycetemcomitans*, GCF-1β (low/high), PG-E2 (low/high), and periodontal disease status (5 levels) will be used in these time to event models. For linear models using fasting glucose 2-hour glucose, and A1-C assays as continuous outcomes, scatter plots will be explored and Pearson’s correlation coefficients will be calculated. Using a linear regression with glucose assessment as a continuous outcome measure, three separate linear models are planned (FG, 2-hour glucose and A1-C). The dependent variables of antibody level (low/high) to periodontal pathogens *P. gingivalis* and *A. actinomycetemcomitans*, GCF-1β (low/high), PG-E2 (low/high), and periodontal disease (yes/no) will be used in the linear regression model. Power calculations using a sample size of 5000 are shown. (Table 6). Since the local inflammatory assessments GCF-1β and PG-E2 databases are one third the size of the antibody assessment sample size, the antibody and periodontal assessment will be the primary analysis, and the analyses of GCF and PG-E2 databases will be used to confirm the primary analysis. All statistical analyses will be conducted using Stata 9.1(Stata, College Station, TX).Models will adjust for confounders such as smoking, tooth loss, age, sex, BMI, sex, race, oxidative stress (8-isoprostane levels), and prior history of cardiovascular events. Assessment of interactions of clinical periodontal disease, cardiovascular disease, and BMI, and oxidative stress are planned (Table 5).
Table 6-Minimal Detectable Differences for Blood Glucose Levels (Primary Outcomes) at Different Power Levels in Planned Linear Regression (Serum antibodies to periodontal pathogens *P. gingivalis* and *A. actinomycetemcomitans* n=5000, alpha=0.05, sd$_1$=standard deviation of assays of population without diabetes, sd$_2$= hypothesized standard deviation of assays in population with high antibody levels=sd$_1$ assuming equal variances)

<table>
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<tr>
<th>Power</th>
<th>FG (mg/dl)</th>
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<td>0.18</td>
</tr>
</tbody>
</table>

sd$_1$=20.5  sd$_2$=66.7  sd$_1$=1.18  sd$_2$=1.18

Limitations:
We expect missing data to vary for each variable in the models and this must be taken into account in the analyses. The models chosen will be inappropriate if the missingness is not missing at random (NMAR). With this longitudinal database, remedies for missing data, such as last value carried forward, again depend on the assumption of the type of missing data. Since the local inflammatory assessments GCF-1β and PG-E2 databases are one third the size of the antibody assessment sample size, the antibody and periodontal assessment will be the primary analysis, and the analyses of GCF and PG-E2 databases will be used to confirm the primary analysis. The small sample sizes, may compromise the precision of the calculated estimates. However, this longitudinal dataset may provide strengthen the evidence from the previous cross-sectional datasets.

References


7. Schmidt, Maria I. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities; a cohort study. Lancet. 1999; 353(1965); 1649-1652.


11. Singer, R.E., Moss, K., Beck, J.D., and Offenbacher, S. Association of Systemic Oxidative Stress with Suppressed Serum IgG to Commensal Oral Biofilm and Modulation by Periodontal Infection, Antiox Redox Sig. Volume 11, Number 12, 2009, 2973-2983.


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

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.csc.unc.edu/ARIC/search.php
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)?

ARIC Manuscript Proposal # 730
PC Reviewed: 06/20/00 Status: A Priority: 2
SC Reviewed: 06/20/00 Status: A Priority: 2

1.a. Full Title: Periodontal disease, diabetes, and atherosclerosis.
b. Abbreviated Title (Length 26 characters): Periodontitis, diabetes & atherosclerosis

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Members of Writing Group:
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Sam Arbes Catherine Champagne Pheobus Madianos
Estelle Riche James Pankow Aaron Folsom

Rationale:
The purpose of the present study is to determine whether periodontal infection in diabetics contributes to the extent of subclinical atherosclerotic disease (as measured by IMT and plaque shadowing) compared to diabetics without periodontal disease and nondiabetics.

Main Hypothesis:
Diabetics with periodontal disease have a higher prevalence of subclinical atherosclerotic disease than diabetics without periodontal disease and non-diabetics.

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

__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/
12. 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.