1.a. **Full Title**: Oxidative Stress and Risk of Diabetes: The ARIC Study

b. **Abbreviated Title (Length 26 characters)**: Ox-LDL and Nitrotyrosine and diabetes risk

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

   **Lead**: Ron C. Hoogeveen, Ph.D.
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   Other writing group members are invited to join.
   (This proposal is based on the ancillary study Inflammatory Precursors of Type 2 Diabetes)

3. **Timeline**: 11/03 – 07/04

4. **Rationale:**

   Type 2 diabetes is associated with increased cardiovascular morbidity and mortality.\(^1\)
   In diabetic patients, postprandial hyperglycemia and hyperlipidemia drive the non-enzymatic
   oxidation and glycation of proteins and lipids, which can lead to a state of increased oxidative
   stress.\(^2\) Experimental studies in cultured cells and animals indicate that oxidative modification
   of LDL enhances its atherogenicity.\(^3\) Plasma levels of oxidized LDL have been shown to be
   significantly higher in patients with coronary artery disease compared to normal controls.\(^4\)
   Furthermore, increased circulating levels of oxidized LDL have been found in diabetic patients
   and in subjects with impaired glucose tolerance.\(^5\)

   Hyperglycemia causes an increased production of nitric oxide (NO) and superoxide anion in
   human aortic endothelial cells,\(^6\) which can lead to the formation of peroxynitrite, a powerful
   oxidant capable of nitrating tyrosine residues in endogenous proteins.\(^7\) Therefore, the presence of
   nitrotyrosine in plasma proteins is considered an indirect marker of oxidative stress.\(^8\) Reactive
   nitrogen species have been shown to be capable of nitrating the tyrosine residues of apo B and
   oxidized LDL recovered from human atherosclerotic aortas contain significantly higher levels of
   nitrotyrosine compared to LDL isolated from plasma of healthy donors.\(^9,10\) Furthermore, a recent
   study showed that nitrotyrosine could be detected in the plasma of all 40 participating Type 2
diabetic patients, but not in 35 healthy control subjects. Although data from numerous studies indicate that oxidized LDL is proinflammatory in nature, there is very limited data available on the relationship of oxidized LDL with either the degree of glucose intolerance or other oxidative stress markers. Therefore, we propose to investigate the association of plasma levels of oxidized LDL and nitrotyrosine with risk for type 2 diabetes.

References:


5. Main Hypothesis/Study Questions:

Plasma levels of ox-LDL and nitrotyrosine are positively and independently associated with incident type 2 diabetes. These associations are stronger in dyslipidemic obese participants compared to normolipidemic lean individuals. Addition of an inflammation score will weaken the associations.

6. Data (variables, time window, source, inclusions/exclusions):
Design: case-cohort study including a random sample of the visit 1 cohort free of diabetes and a random sample of incident diabetes cases ascertained at visits 2-4.
Primary Exposure Data: Oxidized LDL and nitrotyrosine measured on plasma samples from visit 1.
Covariates (from visit 1): age, gender, race, center, fasting glucose, fasting insulin, 2h glucose (visit 4), GAD-antibody, family history of diabetes, physical activity, BMI, WHR, hypertension, cigarette smoking, HDL-C, LDL-C, total cholesterol, triglycerides, NEFA, WBC, fibrinogen, vWF, IL-6, CRP, orosomucoid, sialic acid, adiponectin, leptin, complement C3, ICAM-1, ferritine, hemoglobin, ALT, GGT, medication use (incl. Statins, anti-hypertension and anti-diabetes medication).
Data analysis will include survival analysis with appropriate weighting for the case-cohort design and sampling scheme.

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?  
      ____ 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

   _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)?

11. 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.