1.a. Full Title: Association between family history of type 2 Diabetes Mellitus, the multiple metabolic syndrome (MMS), and the risk of developing type 2 diabetes mellitus

b. Abbreviated Title (Length 26 characters): MMS and incident T2DM

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

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3. Timeline: Analysis of data collected over 4 visits from participants in the ARIC study will begin in December of 2003. A draft of the manuscript will be circulated to the coauthors by July 2004.

4. Rationale:

   Insulin resistance and beta-cell dysfunction are centrally involved in the pathogenesis of type 2 diabetes mellitus (Type 2 DM). Insulin resistance in non-diabetics is known to be a strong predictor of type 2 diabetes, and decline in pancreatic beta-cell function is also known to occur before the development of overt hyperglycemia. Although family history of T2DM is known to be a strong risk factor for insulin resistance, beta cell dysfunction, and the development of the T2DM, recent evidence suggests that family history may be an effect modifier for the association between insulin resistance and T2DM. In a prospective study of 181 normoglycemic people without family history of disease and 150 normoglycemic people with type 2 diabetes in both parents, Goldfine and colleagues found that insulin resistance, as assessed by Intra-venous Glucose Tolerance Test (IVGTT), was a poor predictor of T2DM in individuals with a negative family history of T2DM compared to those with a positive family history of T2DM. This suggests that family history of T2DM may be a surrogate marker for a factor, other than insulin resistance, that is necessary for the for the development of T2DM. Our underlying hypothesis is that the pathogenesis of T2DM consists of two hits – the first hit being the presence of insulin resistance and the second hit being the propensity for beta-cells to fail under insulin resistance. We believe that family history of T2DM is more reflective of
susceptibility to beta-cell dysfunction, hence in individuals with a positive family history of T2DM, insulin resistance is a stronger predictor of T2DM.

Although hyperinsulinemic clamp is widely held by researchers to be the gold standard method for assessing insulin resistance is the hyperinsulinemic clamp, cost and technical complexity prohibit the use of this method in large-scale epidemiology studies, which have often used surrogate markers for insulin resistance, such as elevated serum insulin level, the glucose-to-insulin ratio (also known as the insulinogenic index), the Homeostasis Model of Assessment (HOMA-IR), and the Quantitative Insulin Sensitivity Check Index (QUICKI). For this analysis, we plan to use the aforementioned markers for assessing insulin resistance. Furthermore, as an additional marker of insulin resistance, we plan to use the presence of the MMS syndrome (also referred to in literature as multiple metabolic abnormalities, metabolic syndrome, syndrome X, and the insulin resistance syndrome), which is defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) as clinical identification of at least 3 of 5 metabolic abnormalities including dyslipidemia (defined as triglyceride level ≥ 1.69 mmol/L and/or HDL levels < 1.04/1.29 mmol/L(men/women)), hypertension (systolic/diastolic blood pressure ≥ 130 and/or 85 mmHg), insulin resistance (fasting plasma glucose ≥ 6.1 mmol/L), and obesity (weight circumference > 102/88 cm (men/women)). Finally, we will utilize the HOMA-beta cell index to assess insulin secretion as a marker for beta cell function in order to test the hypothesis that family history of T2DM is associated with the HOMA-beta cell index.

The prospective nature, large sample size, and the availability of various metabolic traits associated with insulin resistance in the African-American and white participants of the ARIC Study provide a unique opportunity to test our hypotheses. A better understanding of the interactions amongst risk factors for T2DM will provide further insight into the model of disease, as well as strengthening the validity of previous findings in small studies. Our proposed analysis has the potential to be instrumental in future efforts to identify “subtypes” of T2DM in order to define phenotypes more precisely for future genetic studies.

5. Main Hypothesis/Study Questions:

Simplified version of the underlying hypothesis:

1. In addition to traditional markers of insulin resistance, including elevated baseline fasting serum insulin level and the HOMA-IR index, the MMS will predict incident T2DM
2. HOMA-beta cell index corrected for severity of insulin resistance will be associated with family history of T2DM.
3. Markers of insulin resistance are stronger predictors of incident T2DM in individuals with a positive family history of T2DM than in those with a negative family history of T2DM.
4. Measures of greater obesity are stronger predictor of incident T2DM in individuals with a negative family history of T2DM than in those with a positive family history of T2DM

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

Exclusions
- prevalent cases of type 2 diabetes at visit 1
- persons missing information on the multiple metabolic syndrome
- persons missing information on family history of diabetes
- people who were lost to followup after visit 1

Data
- visit 1
  - Glucose
  - Total Cholesterol
  - Systolic Blood Pressure (SBP)
  - Body Mass Index (BMI)
  - LDL Cholesterol
  - Family History of Type 2 Diabetes
  - Presence of Type 2 Diabetes in Parents (HOM16B, HOM18B, HOM19B, HOM23B, HOM24B, HOM26B, HOM27B)
-visit 3
  - Insulin
  - Triglycerides
  - Diastolic Blood Pressure (DBP)
  - Waist-to-Hip Ratio (WHR)
  - HDL Cholesterol

Age, sex, race, physical activity, total caloric intake, alcohol intake, smoking
- visit 3
  - Presence of Type 2 Diabetes in Siblings (AMHA24, AMHA 26, AMHA28, AMHA29, AMHA28A, AMHA29, AMHA29A)
- visits 2, 3, 4
  - Incident Type 2 Diabetes

The analysis will use a Cox model with time to diabetes incidence interpolated between the last visit without and the first visit with diabetes (similar to previous papers). Results will be compared to logistic regression modeling incident diabetes as a binary variable. The main analysis will model the risk of diabetes as a function of the metabolic syndrome (using definitions listed previously). Analyses will first be stratified by family history of type 2 diabetes and then combined to test for interaction. Given the large number of incident diabetics and high prevalence of family history we should be able to detect moderate to strong interactions.

New variables will define metabolic syndrome according to the NCEP ATPIII standards. Defining insulin resistance by markers including elevated baseline serum fasting insulin, the HOMA-IR index, the insulinogenic index, and other standards, the association of insulin resistance and incidence of type 2 diabetes will be evaluated. The HOMA-IS (beta cell index), which will be corrected for severity of insulin resistance, will be used to test the association of beta-cell dysfunction with incidence of type 2 diabetes. Additionally, the association of obesity, as defined by BMI and as defined by WHR, and incidence of type 2 diabetes will be tested.

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  ____ 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.csecc.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)?

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.

References


