

ARIC Manuscript Proposal # 968

PC Reviewed: 11/21/03

Status: A

Priority: 2

SC Reviewed: 11/24/03

Status: A

Priority: 2

1.a. Full Title: Antibodies to GAD as a risk factor for developing type 2 diabetes mellitus in middle-aged adults: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): GAD – incident diabetes

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

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3. Timeline:

After approval, the initial analyses and writing will take place in November, 2003, final analyses by February, 2004, final writing and submission of manuscript by May, 2004.

4. Rationale:

Persons at risk of developing insulin-dependent diabetes mellitus (type 1 diabetes) can be recognized by the presence of the glutamic acid decarboxylase (GAD) antibodies (1). GAD antibodies are found in sera from 60%-80% patients at diagnosis or up to 10 years before the diagnosis of type 1 diabetes, and thus are markers of the autoimmune form of the β -cell damage (1;2). These antibodies also occur in some adults with non-insulin-dependent diabetes mellitus (type 2 diabetes) (3). After several months or years, some of these patients become insulin dependent; these are thought to have a slowly evolving form of type 1 diabetes, sometimes called type 1½, or latent autoimmune diabetes in adults (LADA) (1;4). Positivity for GAD antibodies has been shown to be a sensitive and specific marker for future insulin dependency in patients with diabetes (1).

Recently, a high frequency of GAD antibody positivity has been reported in a wide range of ethnic groups and populations. As many as 10-15% of all adults with diabetes may have LADA, which may constitute up to 50% of cases of non-obese, apparently type 2 diabetes (5;6). Several studies showed the prevalence of GAD antibody positivity in different countries and ethnic groups (1;2;7-13). However, no studies have investigated positivity for GAD antibodies as a risk factor to developing diabetes in middle-aged adults.

The objectives of this study are to characterize GAD positivity and cases of LADA in the ARIC Ancillary Study: Inflammatory Precursors of Diabetes; to investigate whether GAD antibody positivity is a risk factor for incident diabetes mellitus in middle-aged adults; and to compare risk factors for the development of diabetes mellitus in persons positive and negative for GAD antibodies, with attention to the extent to which inflammation markers are risk factors for developing diabetes in subjects with antibodies for GAD.

5. Main Study Questions:

- (1) To estimate the prevalence of GAD positivity, separately for African-Americans and whites, in the cohort random sample
- (2) To characterize the incident cases of LADA in terms of sociodemographics and risk factor profile in the ARIC study, in general and by ethnic group.
- (3) To describe the crude and independent associations of antibodies to GAD with incident diabetes in middle-aged adults.
- (4) To compare risk factors, including an inflammation score, for the development of diabetes mellitus in middle-aged adults GAD+ as compared with those GAD-.

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

- (1) Antibody GAD variables: GAD, GADNUM and GADPOS
- (2) Outcome: Time to develop incident diabetes (FUTIMEDM)
- (3) Diabetes status: Incident diabetes status (DIABCASE).
- (4) Demographic variables: age, gender, ethnicity
- (5) Other diabetes risk factors at visit 1: hypertension (HYPERT05), family history of diabetes (FHDMM) body mass index (BMI01), waist-to-hip ratio (WSTHPR01), glucose level (GLUCOS01), cigarette smoking status, hypertensive medication use.
- (6) Inflammation markers: IL6, CRP, AGP, SIAL, HEMA09, HMTA03.

7. Analysis plan

- ✓ Descriptive analysis of the main variables through graphics and summary statistics, for all subjects and stratified by GADPOS status.
- ✓ Risk modelling through proportional hazard models, initially considering just the GADPOS exposure, weighted to account for sampling fraction, as in MS#853, and then including covariates.
- ✓ After stratifying the dataset in GAD+ and GAD- at baseline, identifying and comparing risk factors for the development of DM in those GAD+ vs. GAD- (proportional hazard model weighting as in MS#853). Sample size will not permit formal testing of interactions of GAD positivity with other risk factors in associations with incident diabetes.
- ✓ All analyses will be done using SAS and SUDAAN.

7.a. Will the data be used for non-CVD analysis in this manuscript? ☐ Yes ☒ No

b. If Yes, is the author aware that the file ICTDER01 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 ICTDER01 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 ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☐ Yes ☒ No

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