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Original article

Diabetes-related factors and abdominal aortic aneurysm events: the Atherosclerotic Risk in Communities Study

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ABSTRACT

Purpose: To test the hypothesis that diabetes-related factors (metabolic syndrome [MetS], glucose, insulin, and leptin) are inversely associated with abdominal aortic aneurysm (AAA) risk.
Methods: We followed 13,736 participants, aged 45–64 years, without prior AAA surgery at baseline (1987–1989), for AAA occurrence through 2011. Hazard ratios (HRs) and their 95% confidence intervals (CIs) of AAA were calculated using Cox regression.
Results: During 275,054 person-years of follow-up, we identified 518 AAA events. Fasting serum glucose was associated inversely with AAA risk (HR [95% CI] per one unit increment in $\log_2$(glucose), 0.54 [0.36–0.80]), but fasting insulin was not associated with AAA. Plasma leptin was also associated inversely with AAA occurrence (HR [95% CI] per one unit increment in $\log_2$(leptin), 0.83 [0.71–0.98]). Compared with individuals without MetS, those with MetS had increased risk of AAA (HR [95% CI], 1.24 [1.04–1.48]). Among individuals with or without diabetes, the HRs increased monotonically with a greater number of non-glucose MetS components.
Conclusions: Diabetes, fasting glucose, and plasma leptin were inversely associated with risk of AAA. In contrast, the MetS was associated with increased risk of AAA, due to the influence of the non-glucose MetS components.

Introduction

Abdominal aortic aneurysm (AAA) is an important cause of death in Western countries, especially in old age [1,2]. Several risk factors for AAA have been identified, including atherosclerosis, old age, male sex, hypertension, dyslipidemia, and smoking [1]. In contrast, diabetes mellitus (DM), surprisingly, is inversely associated with AAA risk [3–5]. In addition, a previous study suggested obesity might also be inversely associated with AAA [6], although this appears controversial [7,8]. Obesity is closely related to DM, and thus other DM-related factors such as blood insulin concentrations or the metabolic syndrome (MetS) might also be inversely associated with AAA risk. To date, there is no prospective study investigating the association of these DM-related factors with AAA.

The Atherosclerosis Risk in Communities (ARIC) study measured on its cohort several DM-related variables—MetS, fasting serum glucose and insulin, and plasma leptin [9]—and has identified incident, clinical AAAs through 2011. Therefore, the primary and secondary objectives of this study were to examine the association of MetS and those plasma biomarkers with AAA risk, respectively.

Materials and methods

Study design, setting, and population

The ARIC study recruited 15,792 mostly white or African American men and women aged 45–64 from four US communities (Jackson, Mississippi [African Americans only]; Washington County, Maryland; suburbs of Minneapolis, Minnesota; and Forsyth County, North Carolina) to a baseline examination between 1987 and 1989 [10]. Major cardiovascular risk factors were measured through home interview and clinic examinations. This study was conducted according to the guidelines of the Helsinki Declaration.

Disclosures: All authors have approved the final article.
The authors have no conflict of interest to declare.

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In the present analyses, we excluded participants who at baseline in 1987–1989 reported prior AAA surgery or aortic angioplasty ($n = 11$), had uncertain AAA status during follow-up ($n = 30$), were non-white participants in Washington County or Minneapolis or non-white/black participants in Forsyth County ($n = 48$) to allow multivariable adjustment for race and study site [11], or were participants whose data on main exposures (MetS and fasting glucose and insulin; $n = 927$) or any other covariates ($n = 1013$) were missing. After exclusions, 13,763 participants were included in the present analyses. For the leptin analysis, after identical exclusions, 701 participants were available. Assuming the sample size of our participants, the estimated proportion of AAA cases in the reference group ≥ 0.01, type I error $= 0.05$, relative risk $= 0.5$ (decreased risk) or 2.0 (increased risk), and $\geq$20 years of follow-up, we obtained study power ≥ 0.8.

The institutional review boards of the collaborating universities approved the protocol, and ARIC obtained written informed consent from all participants.

Exposure and covariates

DM was defined as a fasting serum glucose $\geq$126 mg/dL, nonfasting serum glucose $\geq$200 mg/dL, a self-reported physician diagnosis of diabetes, or on treatment for DM in the past 2 weeks [12]. MetS was defined by the presence of at least three of the following components: (i) central obesity, waist circumference $\geq$ 102 cm in men or $\geq$ 88 cm in women; (ii) low high-density lipoprotein (HDL) cholesterol, plasma HDL $<$ 1.0 mmol/L in men and $<$ 1.3 mmol/L in women or on lipid medication; (iii) hypertension, systolic blood pressure $\geq$ 130 mm Hg or diastolic blood pressure $\geq$ 85 mm Hg or on antihypertensive medication; (iv) hypertriglyceridemia, plasma triglycerides $\geq$ 1.7 mmol/L or on lipid medication; and (v) abnormal glucose metabolism, fasting serum glucose $\geq$ 100 mg/dL or on treatment for DM [13]. Glucose was measured by a hexokinase method on a Coulter DACOS analyzer (Coulter Instruments, Fullerton, CA), and insulin was measured with a commercial radioimmunoassay (Cambridge Biomedical, Billerica, MA) [14]. Based on our internal quality control materials, the interassay analytical standard deviation was 1.3 mg/dL (percent coefficient of variation, 1.6%) at 79.3 mg/dL for glucose and 16.5 mU/L (percent coefficient of variation, 17%) at 96.9 mU/L for insulin [14]. Plasma leptin (reliability coefficient based on split specimens was 0.94) had been measured in duplicate by direct sandwich ELISA (LINCO Research, Inc., St Charles, MI) [9] in a previous nested case-cohort study of incident coronary heart disease from ARIC visit 1 to December 31, 1993. The cohort reference group, the focus of the present leptin analysis, was a stratified random sample of participants free of baseline coronary heart disease in the ARIC cohort, with oversampling of participants with thin average carotid intima-media thickness measurements at baseline ($<$30th percentile) and different sampling fractions by age, sex, and race [15].

We also included in analysis other risk factors (covariates) for AAA in ARIC [8,16], including age, sex, race (white or African American), height (cm), smoking status (current, former, or never), pack-years of smoking, plasma low-density lipoprotein cholesterol, and history of peripheral artery disease.

Identification of AAA

ARIC identified incident clinical AAAs by several strategies [8,16]. During annual telephone calls, ARIC participants were asked about any interim hospitalizations and participants' deaths were identified. Surveillance of local hospitals was also conducted to identify additional hospitalizations or deaths. Moreover, participant identifiers were linked with fee-for-service Medicare data from the Centers for Medicare and Medicaid Services, to find additional hospital or outpatient AAA events for participants over 65 years. ARIC identified incident clinical AAAs as those with a hospital discharge diagnosis from any source, or two Medicare outpatient claims that occurred at least 1 week apart, with International Classification of Diseases (*ICD*)-*9*-*CM* codes of 441.3 or 441.4, or procedure codes of 38.44 or 39.71, or death codes, *ICD*-*9* 441.3 or 441.4 or *ICD*-*10* code I71.3 or I71.4. AAAs based on procedure codes were required to be verified by diagnosis codes. Some of these clinical diagnoses would include asymptomatic AAAs that happened to be clinically documented.

Statistical analysis

SAS, version 9.4, software (SAS Institute Inc., Cary, NC) was used for statistical analyses. All statistical tests were two tailed, and P values $<$ .05 were regarded as significant.

We computed mean levels or percentages of potential AAA risk factors at baseline according to the presence or absence of DM. Person-years of follow-up was calculated from baseline to the first endpoint: AAA, death, loss to follow-up, or administrative censoring at December 31, 2011. Hazard ratios (HRs) and their 95% confidence intervals of clinical AAA were calculated after adjustment for other AAA risk factors using Cox proportional hazards model (for leptin analysis, stratified sampling weights using a weighted Cox proportional hazard models were used to account for sampling). The proportional hazards assumption in the Cox regression was tested using risk factor-by-time interactions and was not violated. Because we found no statistical interactions between sex or race and DM-related factors in relation to AAA risk, we pooled the analysis across sex and race. Plasma fasting glucose and insulin and leptin were modeled using continuous variables, with $\log_2$-transformed values because of skewness.

For sensitivity analyses, we (i) further adjusted for abnormal glucose metabolism (fasting serum glucose $\geq$ 100 mg/dL or on treatment for DM) for the analysis of the associations between the number of MetS components and risk of AAA and (ii) reran models for this analysis after changing the definition of the reference group from the number of MetS components, 0–1 to 0 or 0–2.

Results

Baseline characteristics of study participants by diabetes

Compared with individuals without DM, those with DM tended to be older, male, African American, shorter in stature, and noncurrent smokers, have more pack-years of smoking, more hypertension and peripheral artery disease, and have a lower HDL cholesterol level and a higher low-density lipoprotein cholesterol level (Table 1). Prevalence or means of the DM-related factors of interest were higher in individuals with DM than those without DM.

Associations between diabetes-related biomarkers and risk of AAA

During the 275,054 person-years of follow-up for the 13,763 participants, we identified 518 incident clinical AAA events. Individuals with DM had a lower risk of AAA, and this association remained significant even after adjusting for competing risks of death from underlying causes other than AAA (Supplemental Table 1). A fully adjusted model (model 2) showed that fasting serum glucose and plasma leptin were inversely associated with AAA risk, but fasting serum insulin was not associated with AAA risk (Table 2). After excluding individuals with DM, fasting glucose