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Fasting and post-glucose load measures of insulin resistance and risk of incident atrial fibrillation: The Cardiovascular Health Study

P.K. Garg [a,*], M.L. Biggs [b], R. Kaplan [c], J.R. Kizer [c,d], S.R. Heckbert [e], K.J. Mukamal [f]

[a] Division of Cardiology, University of Southern California Keck School of Medicine, Los Angeles, CA, USA
[b] Department of Biostatistics, University of Washington, Seattle, WA, USA
[c] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA
[d] Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA
[e] Department of Epidemiology, University of Washington, Seattle, WA, USA
[f] Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

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Abstract *Background and aims:* Existing literature in individuals without diabetes has not demonstrated a relationship between IR and incident AF; however, data are limited and only fasting glucose measures of IR were assessed. We evaluated the relationship of both fasting and post-glucose load IR measures with the development of atrial fibrillation in nondiabetic older adults.

Methods and results: Among Cardiovascular Health Study participants, a population-based cohort of 5888 adults aged 65 years or older enrolled in two waves (1989–1990 and 1992–1993), those without prevalent AF or diabetes and with IR measures at baseline were followed for the development of AF, identified by follow-up visit electrocardiograms, hospital discharge diagnosis coding, or Medicare claims data, through 2014. Fasting IR was determined by the homeostatic model of insulin resistance (HOMA-IR) and post-glucose load IR was determined by the Gutt index. Cox proportional hazards models were used to determine the association of IR with risk of AF. Analyses included 3601 participants (41% men) with a mean age of 73 years. Over a median follow-up of 12.3 years, 1443 (40%) developed AF. After multivariate adjustment, neither HOMA-IR nor the Gutt index was associated with risk of developing AF [hazard ratios (95% confidence intervals): 0.96 (0.90, 1.03) for 1-SD increase in HOMA-IR and 1.03 (0.97, 1.10) for 1-SD decrease in the Gutt index].

Conclusions: We found no evidence of an association between either fasting or post-glucose load IR measures and incident AF.

Introduction

Atrial fibrillation (AF) is the most commonly presenting cardiac arrhythmia in clinical practice, with a prevalence of over 2 million people in the United States alone, and is a major source of cardiovascular morbidity and mortality [1–4]. Established risk factors for AF only account for approximately half of the AF cases in the population and the pathophysiology of AF is still incompletely understood [4–6]. A better understanding of AF disease mechanisms and identification of additional risk factors are important.

Insulin resistance (IR) is closely associated with diabetes, inflammation, and obesity [7–9]. Diabetes has ostensibly been established as a risk factor for AF in prior

* Corresponding author. 1510 San Pablo St. Suite 322, Los Angeles, CA, 90033, USA. Fax: +1 323 442 6133.
E-mail address: parveeng@med.usc.edu (P.K. Garg).

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prospective studies, including the Cardiovascular Health Study (CHS), as part of risk prediction models [10]. Metabolic syndrome, a condition characterized by the presence of IR, has also been associated with AF in prospective studies [11–13]. Previous studies in individuals without underlying diabetes, however, have been unable to demonstrate a relationship between IR and incident AF [14,15]. Participants from both of these studies were relatively young (mean age <60 years) with a relatively low prevalence of comorbidities including hypertension and obesity.

These studies also relied only on fasting glucose measures of IR, which reflects hepatic IR, and did not assess post-glucose load measures of IR, which reflects peripheral or whole-body IR. Impaired glucose tolerance has been more strongly associated with development of vascular disease than impaired fasting glucose [16,17]. Similarly, measures that capture peripheral IR may demonstrate a stronger association than hepatic measures with the development of AF. Considering that IR and risk factors for AF are closely related and recognizing the limitations of prior studies, we sought to determine the association of both fasting and post-glucose load measures of IR with incident AF in an older population without diabetes at baseline.

Methods

Study participants

The CHS is a community-based, longitudinal observational study of adults aged 65 and older at baseline designed to evaluate risk factors for the development and progression of cardiovascular disease. The study's primary objectives and design have been reported previously [18,19]. An initial cohort of 5201 individuals was recruited in 1989–1990, and a supplemental cohort of 687 predominantly African American participants were recruited in 1992–1993. The CHS received approval from institutional review boards of all participating centers and all participants provided written informed consent. Self-reported health behaviors, history of diseases, anthropometric measures, current medication use, seated blood pressure readings, electrocardiogram recordings, and fasting blood chemistry measures were obtained during the baseline interview and clinical examination.

We included participants who at baseline were free of diabetes, had no history of AF, and had fasting and 2-h oral glucose tolerance test insulin and glucose measurements. Since post-glucose loading measures were first performed in 1996–97 for the supplemental cohort, this served as their baseline visit for this analysis (n = 575). We excluded 215 participants who at baseline had a history of AF, 1219 participants who had diabetes, and 231 participants who were missing at least 1 fasting or 2-h insulin or glucose measurement. Due to the concern for suspected AF, we excluded another 510 participants with a pacemaker or on either digoxin or anti-arrhythmic drug therapy; this left 3601 participants for analysis.

Insulin and glucose measures

Serum samples were obtained after an overnight fast of at least 8 h, and again 2 h after a 75-g oral glucose challenge. Insulin was measured with a competitive radioimmunoassay (Diagnostic Products Corporation), and glucose was measured with an enzymatic method [20]. Fasting measures were obtained at study examinations in 1989–1990 (original cohort only), 1992–1993, and 1996–1997. Post-glucose loading measures were obtained at in 1989–90 (original cohort only) and 1996–97.

The homeostatic model of insulin resistance (HOMA-IR) is a measure of fasting IR calculated using the following formula: [fasting glucose (mmol/l)] × [fasting insulin (U/ml)]/22.5 [21]. The Gutt insulin sensitivity index (Gutt ISI) is a measure of post-glucose loading IR and calculated as insulin sensitivity = $m/(G \times \mathrm{I})$, where m is a measure of glucose uptake during the OGTT calculated from body weight and from fasting and 2-h glucose, G is the mean of fasting and 2-h glucose, and I is a $\log_{10}$ transformation of the mean of fasting and 2-h insulin. Units for the Gutt index are (mg × L [2])/(mmol × mU × min) [22,23]. The Matsuda insulin sensitivity index (Matsuda ISI) is a second measure of post-glucose loading IR and is calculated as insulin sensitivity = $\sqrt{(10{,}000/(G_0 \times I_0 \times G_{120} \times I_{120})}$, where G_0 is glucose concentration (mg/dl) at time 0, I_0 is the insulin concentration at time 0 (mmol/ml), G_{120} is the glucose concentration at time 120 min, and I_{120} is the insulin concentration 120 min obtained from an OGTT [24].

Atrial fibrillation

AF was identified from 3 sources: (1) outpatient ECGs obtained yearly at study examinations through 1998–1999 and interpreted by the EPICARE ECG reading center [25]; (2) hospital discharge diagnoses with ICD-9 codes for AF or atrial flutter (427.31, 427.32) found through CHS hospitalization surveillance, excluding diagnoses assigned during the same hospitalization as coronary artery bypass or heart valve surgery, and (3) Medicare claims for inpatient care, outpatient care, and physician visits with ICD-9 codes for AF or atrial flutter.

Covariates

Age, gender, race, smoking status, alcohol consumption, and physical activity were obtained by self-report. Recent medication use was assessed using a medication inventory [26]. Smoking status was categorized as current, former, and never use. Alcohol consumption referred to number of alcoholic drinks consumed per week. Physical activity levels referred to the energy in kilocalories expended in weekly household and leisure-time physical activity estimated from the Minnesota Leisure Time Activities Questionnaire.

Field center staff directly measured waist circumference, weight, and standing height. Body mass index was calculated as measured weight in kilograms divided by

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