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Fasting and Post-Glucose Load Measures of Insulin Resistance and Risk of Incident Atrial Fibrillation: The Cardiovascular Health Study

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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].

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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 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 5,201 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-hour 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-hour 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 hours, and again 2 hours 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=$m/(G*I)$, where m is a measure of glucose uptake during the OGTT calculated from body weight and from fasting and 2-hour glucose, G is the mean of fasting and 2-hour glucose, and I is a $\log_{10}$ transformation of the mean of fasting and 2-hour 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=$\sqrt{(10{,}000/(G_0*I_0*G_{120}*I_{120})}$, 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 minutes, and I_{120} is the insulin concentration 120 minutes 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 standing height in meters squared. Diabetes was defined as use of insulin or oral hypoglycemic drugs, fasting serum glucose ≥126 mg/dL, random serum glucose ≥200 mg/dL, or 2-hour serum glucose ≥200 mg/dL. Hypertension was defined as: 1) systolic blood pressure ≥140, diastolic ≥90 mmHg, or both or 2) self-report of physician-diagnosed hypertension accompanied by use of medications for hypertension. C-reactive protein (CRP) was measured by an in-house validated high-sensitivity enzyme-linked immunosorbent assay (ELISA)[20] with an inter-assay coefficient of variation of 6%.[27]

Coronary heart disease (CHD) and heart failure (HF) were identified by self-report or linkage with Medicare hospitalization data, and confirmed by physician adjudication using information obtained from the baseline examination, medical records, and physician questionnaires.[28] CHD was defined as having a history of one or more of the following: myocardial infarction, angina, coronary artery bypass surgery or angioplasty.

Statistical Analysis

Descriptive statistics (mean and standard deviation for continuous variables and counts and percentages for categorical variables) were used to describe baseline characteristics of participants stratified by quartiles of Gutt insulin sensitivity index levels.

Adjusting for field center, enrollment wave, sex, race, and height, Cox proportional hazards models were used to investigate the associations of individual components used for calculating IR—fasting glucose, fasting insulin, 2-hour glucose, 2-hour insulin, and body weight—with incident AF separately (Model 1). We subsequently adjusted for waist circumference, smoking, alcohol, CHD, HF, systolic BP, and anti-hypertension medications (Model 2). In this analysis, we modeled these components continuously (per 1 standard deviation (SD) increment) and also categorized into quartiles (Referent=1st quartile).

Adjusting for the same variables mentioned above, Cox proportional hazards models were then used to investigate the association of IR measures (HOMA-IR, Gutt ISI, Matsuda ISI) with incident AF. IR measures were modeled continuously (HOMA-IR per 1 SD increment; Gutt and Matsuda ISI per 1 SD decrement), after testing for non-linearity, and also categorized into quartiles (Referent=1st quartile for HOMA-IR; 4th quartile for Gutt and Matsuda ISI). For initial cohort participants without AF by year 9 and with fasting glucose and/or post-glucose load measures at year 9, IR values were updated at year 9 for this analysis by using an average of year 2 & 9 values. For individuals who developed treated diabetes but not AF at year 9 (n=129), their year 9 IR values were set to the 99th percentile.

Finally, we evaluated the association of baseline diabetes and development of AF in the entire cohort, adjusting for the same variables mentioned above, to provide a comparison with baseline IR and incident AF associations in non-diabetic individuals. In this analysis, only CHS participants with a history of AF were excluded.

Results

Mean age for included participants was 72.6 years, 41% were male, and 9% were black. Over a median follow-up of 12.3 years, 1443 (40%) participants developed AF. Table 1 reports participant characteristics across categories (quartiles) of baseline Gutt ISI. Compared to participants in the lowest IR category (highest insulin sensitivity), those in higher IR categories were older, less likely to smoke, and more likely to have CHD, to have HF, and be on anti-hypertensive medications. Baseline body mass index, systolic blood pressure, diastolic blood pressure, and C-reactive protein were higher, while physical activity was lower, in participants with higher IR values as defined by the Gutt ISI.

Table 2 shows the risk of incident AF according to the individual IR components. Compared to participants in the lowest quartile of the individual IR components, those in higher quartiles of their respective components were not at a significantly higher risk of incident AF in multivariate adjusted analysis.

Associations of IR measures with risk of incident AF are shown in Table 3. Each 1-SD decrease in the Gutt index was associated with an increased risk of AF after adjustment for age, race, gender, field center, enrollment wave, and height (hazard ratio (HR) 1.06; 95% confidence interval (CI) 1.00, 1.12); however, this association was substantially attenuated and no longer statistically significant after additional adjustment for waist circumference, smoking, alcohol, CHD, HF, systolic blood pressure, and anti-hypertension medication use (HR: 1.03, 95% CI: 0.97, 1.10). No significant associations were noted in minimally adjusted or fully adjusted models for HOMA-IR or Matsuda ISI with risk of AF.

We determined the association of baseline diabetes with the development of AF in the entire cohort to provide a comparison with baseline IR and incident AF associations in non-diabetic individuals. Diabetes was associated with a 18% increased risk of incident AF after adjustment for age, race, gender, field center, enrollment wave, and height (HR: 1.18, 95% CI: 1.05, 1.32); however, this association was attenuated and not statistically significant after additional adjustment for clinical variables (HR: 1.07, 95% CI: 0.95, 1.20).

Discussion

In a large community-based cohort of older adults we found no association of either fasting or post-glucose load IR with an increased risk of incident AF in multivariate adjusted models. No significant relationships were observed for any of the individual IR components with development of AF as well.

Although a lack of association has already been reported between fasting IR measures and AF,[14,15] it was important to determine whether findings were similar or different for post-glucose load IR measures. IR is a condition where three primary metabolic tissues, skeletal muscle, liver, and adipose tissue, become less sensitive to insulin and its downstream metabolic actions under normal serum glucose concentrations.[29] Post-glucose load and fasting IR demonstrate different patterns of insulin sensitivity and release and may capture IR in certain metabolic tissue types better than others.[30] Post-glucose load IR is a peripheral measure that mainly measures skeletal muscle and adipose tissue glucose uptake in response

to insulin while fasting IR is a central measure that assesses hepatic tissue glucose uptake in response to insulin. Given that skeletal muscle and adipose tissue IR are important determinants of increased free fatty acid levels and ectopic fat deposition, it is important to assess their potential effects separately from those of hepatic IR.[31] These two IR measures are still strongly correlated, however, and trying to differentiate based on fasting and post-glucose load measures in epidemiologic studies is challenging.[32]

The lack of an association between IR measures and incident AF may be due to the fact that much of the higher risk thought to be associated with AF is actually related to its close relationship with more established risk factors including obesity and hypertension.[33–37] Diabetes was associated with incident AF in a model adjusted only for age, sex, race, field center, enrollment wave, and height; however, this association was attenuated after adjustment for additional clinical risk factors. Metabolic syndrome, although a condition characterized by IR, is defined, in part, by the presence of hypertension and obesity.[11–13] Obesity, in particular, induces a chronic low-grade inflammation state resulting in increased expression of inflammatory cytokines and activation of signaling pathways that disrupt insulin signaling and action.[38] This process contributes to the development of IR, which is considered a precursor to diabetes.[39,40] Similarly, after expanding our cohort to include diabetic subjects, the association between diabetes and incident AF was also attenuated after adjustment for clinical variables. A prior meta-analysis of cohort and case-control studies also noted that greater levels of adjustment reduced the effect size for the association between diabetes and risk of AF.[41]

The strengths of the study include its prospective design with a median follow-up greater than 10 years, simultaneous assessment of both fasting and post-glucose load IR measures, and inclusion of repeated IR measures. Our study also has limitations. Participants in the CHS are over the age of 65 years, which limits the generalizability of our findings to younger participants; however, results were similar in a substantially younger cohort of Framingham Heart Study participants whose mean age was 59 years. AF events were not adjudicated and relied in part on hospital discharge codes.[14] This may have resulted in under-ascertainment of AF events, especially for AF that was paroxysmal or asymptomatic. Lastly, fasting and 2-hour measures of IR modestly correlate with directly measured IR; however, invasive glycemic clamp testing places a large burden on research participants and is impractical in epidemiologic study.[42] In conclusion, we found no evidence of an association between either fasting or post-glucose load IR measures and incident AF.

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Table 1.

Baseline characteristics of CHS participants according to quartiles of Gutt insulin sensitivity index (mg·L2/mmol·mU·min)

Characteristic *	←Less insulin resistant		More insulin resistant→		
	>76.41 (n=900)	**>59.8–76.41 (n=900)**	**>47.14–59.8 (n=900)**	**≤47.14 (n=901)**	***p*-trend** †
Age	72.0 (5.2)	72.7 (5.6)	72.7 (5.4)	72.9 (5.5)	<0.01
Male, %	401 (45%)	345 (38%)	345 (38%)	387 (43%)	0.51
Black, %	73 (8%)	84 (9%)	84 (9%)	89 (10%)	0.22
Smoking status, %					
Never	372 (42%)	428 (48%)	418 (47%)	432 (48%)	
Former	387 (43%)	355 (39%)	370 (41%)	388 (43%)	
Current	129 (14%)	113 (13%)	101 (11%)	75 (8%)	<0.01
Alcoholic drinks per week	3.0 (6.3)	3.5 (21.9)	2.9 (7.3)	2.6 (7.0)	0.31
Prevalent coronary heart disease †, %	140 (16%)	113 (13%)	135 (15%)	174 (19%)	0.01
Prevalent heart failure †, %	9 (1%)	14 (2%)	12 (1%)	23 (3%)	0.02
BMI, kg/m^2	24.6 (3.7)	25.4 (4.0)	26.5 (4.1)	28.3 (4.8)	<0.01
SBP, mmHg	129.9 (22.0)	134.2 (20.4)	135.6 (20.5)	137.5 (20.9)	<0.01
DBP, mmHg	69.7 (11.1)	69.7 (10.7)	70.8 (11.3)	71.4 (11.3)	<0.01
Physical activity, kcal/week	2056 (2158)	1844 (2034)	1868 (2092)	1725 (2106)	<0.01
C-reactive protein, mg/L	3.1 (5.0)	3.9 (7.8)	4.1 (6.7)	4.5 (6.1)	<0.01
Anti-hypertensive use, %	290 (32%)	320 (36%)	336 (37%)	464 (52%)	<0.01

CHS=Cardiovascular Health Study, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure

*Continuous variables are expressed as mean (SD). Categorical variables are N (percent).

†Tests for trend were conducted using linear regression for continuous variables and a nonparametric test for trend across ordered groups for categorical measures.

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Table 2.

Associations of individual insulin resistance components with incident atrial fibrillation among CHS participants [*]

Component	AF Cases	Incidence of AF (per 1000 person-years)	Model 1[†] HR (95% CI)	Model 2[‡] HR (95% CI)
Fasting glucose (mg/dL)				
≤92	368	29.5	1 (Referent)	1 (Referent)
>92–98	388	31.1	1.05 (0.90–1.22)	1.03 (0.89–1.20)
>98–104	336	31.7	1.06 (0.90–1.24)	0.98 (0.83–1.15)
>104	351	33.1	1.10 (0.94–1.28)	0.99 (0.83–1.17)
Per SD			1.02 (0.96–1.08)	0.97 (0.92–1.03)
Fasting insulin (IU/ml)				
≤9	315	30.1	1 (Referent)	1 (Referent)
>9–12	436	32.3	0.94 (0.80–1.09)	0.89 (0.76–1.04)
>12–16	372	31.9	0.95 (0.81–1.11)	0.85 (0.72–1.01)
>16	320	30.4	0.94 (0.80–1.11)	0.78 (0.65–0.95)
Per SD			1.01 (0.96–1.08)	0.96 (0.90–1.03)
2-h glucose (mg/dL)				
≤92	221	25.0	1 (Referent)	1 (Referent)
>92–98	178	24.4	1.11 (0.90–1.36)	1.13 (0.92–1.40)
>98–104	212	27.5	1.20 (0.98–1.45)	1.20 (0.98–1.47)
>104	832	37.4	1.03 (0.87–1.22)	1.01 (0.85–1.20)
Per SD			1.06 (1.00–1.11)	1.04 (0.99–1.10)
2-h insulin (IU/ml)				
≤40	336	32.3	1 (Referent)	1 (Referent)
>40–64	399	32.1	0.96 (0.82–1.12)	0.92 (0.79–1.08)
>64–100	368	30.2	0.95 (0.81–1.11)	0.87 (0.74–1.03)
>100	340	30.6	1.00 (0.85–1.17)	0.90 (0.76–1.07)
Per SD			0.98 (0.93–1.04)	0.95 (0.89–1.01)
Weight (lbs)				
≤133	330	29.3	1 (Referent)	1 (Referent)

Component	AF Cases	Incidence of AF (per 1000 person-years)	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
>133–155	348	29.4	0.98 (0.83–1.16)	0.98 (0.81–1.18)
>155–176	363	30.6	1.01 (0.84–1.20)	0.95 (0.76–1.18)
>176	402	35.9	1.18 (0.97–1.43)	1.05 (0.78–1.40)
Per SD			1.09 (1.02–1.17)	1.08 (0.95–1.22)

AF=atrial fibrillation, HR=hazards ratio, CI=confidence interval

*Results of multivariable Cox proportional hazards models

†Model 1 adjusted for field center, enrollment wave, age, sex, race, and height

‡Model 2 adjusted for field center, enrollment wave, age, sex, race, height, waist circumference, smoking, alcohol consumption, coronary heart disease, heart failure, systolic BP, and anti-hypertension medications

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Table 3.

Associations of HOMA-IR, Gutt ISI, and Matsuda ISI with incident atrial fibrillation among CHS participants [*]

Component	AF Cases	Incidence of AF (per 1000 person-years)	Model 1[†] HR (95% CI)	Model 2[‡] HR (95% CI)
HOMA-IR				
≤2.18	336	32.1	1 (Referent)	1 (Referent)
>2.18–2.87	374	29.9	0.85 (0.72–0.99)	0.78 (0.67–0.92)
>2.87–3.96	390	33.1	0.96 (0.83–1.12)	0.85 (0.72–1.00)
>3.96	343	30.2	0.92 (0.79–1.08)	0.76 (0.63–0.91)
Per SD[**]			1,02 (0.96–1.08)	0.96 (0.90–1.03)
Gutt ISI (mg·L2/mmol·mU·min)				
>76.41	337	28.7	1 (Referent)	1 (Referent)
>59.8–76.41	412	34.4	1.17 (1.01–1.37)	1.15 (0.98–1.34)
>47.14–59.8	362	30.7	1.11 (0.95–1.30)	1.06 (0.90–1.25)
≤47.14	332	31.3	1.17 (0.99–1.37)	1.09 (0.92–1.30)
Per SD[**]			1.06 (1.00–1.12)	1.03 (0.97–1.10)
Matsuda ISI				
>4.85	344	29.7	1 (Referent)	1 (Referent)
>3.29–4.85	398	32.7	1.10 (0.95–1.28)	1.05 (0.90–1.23)
>2.21–3.29	381	32.7	1.17 (1.00–1.37)	1.09 (0.92–1.28)
≤2.21	320	29.8	1.12 (0.96–1.32)	1.02 (0.85–1.22)
Per SD[**]			1.03 (0.97–1.09)	0.99 (0.93–1.05)

HOMA-IR=homeostatic model of insulin resistance, ISI=insulin sensitivity index, AF=atrial fibrillation, HR=hazards ratio, CI=confidence interval

[*] Results of multivariable Cox proportional hazards models

[†] Model 1 adjusted for field center, enrollment wave, age, sex, race, and height

[‡] Model 2 adjusted for field center, enrollment wave, age, sex, race, height, waist circumference, smoking, alcohol, coronary heart disease, heart failure, systolic BP, and anti-hypertension medications

[**] Per SD increase for HOMA-IR; Per SD decrease for Gutt and Matsuda ISI