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Insulin Resistance and Atrial Fibrillation (From the Framingham Heart Study)

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Abstract

Diabetes mellitus and obesity are increasing in prevalence and are associated with an elevated risk of atrial fibrillation (AF). Given the aging of the US population, AF is projected to concomitantly increase in prevalence in the upcoming decades. Both diabetes and obesity are associated with insulin resistance. Whether insulin resistance is an intermediate step for the development of AF is uncertain. We hypothesized that insulin resistance is associated with an increased risk of incident AF. We examined the association of insulin resistance with incident AF using multivariable Cox proportional hazards regression adjusting for established AF risk factors (age, sex, systolic blood pressure, hypertension treatment, PR interval, significant heart murmur, heart failure and body mass index). Of the 3,023 eligible participants (55% women; mean age 59 years) representing 4,583 persons-examinations (Framingham Offspring 5th and 7th examination cycles), 279 individuals developed AF (9.3%) up to 10 years of follow-up. With multivariable modeling, insulin resistance was not significantly associated with incident AF (hazard ratio comparing the top with the other three quartiles of homeostatic model assessment index (HOMA) 1.18, 95%

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confidence interval 0.84 to 1.65, $p = 0.34$). In a community-based cohort with up to 10 years follow-up, no significant association was observed between insulin resistance and incident AF.

Keywords

Insulin resistance; atrial fibrillation; risk factors; epidemiology

Insulin resistance is a common metabolic substrate that is associated with several cardiovascular conditions.^{1,2} In addition, insulin resistance is associated with inflammation, diabetes, and obesity, all common risk factors for AF.^{3–6} Given the association of insulin resistance with the metabolic syndrome and with risk factors for AF, we hypothesized that insulin resistance predisposes to AF. We used the homeostasis model assessment index for insulin resistance (HOMA-IR), a validated research tool of insulin resistance to examine the relation of insulin resistance to incident AF in the community.

Methods

We evaluated Framingham Heart Study Offspring who attended either the fifth (1991–1994) or seventh (1998–2001) examination cycles (total possible person examinations=7338). Enrollment details have been described extensively elsewhere.⁷ We excluded 1,580 participants under the age of 50 years (low risk of incident AF), 214 with prevalent AF, 588 with prevalent diabetes (in which the insulin levels are not informative), and 373 participants with missing HOMA-IR at both examinations. The Institutional Review Board at Boston University Medical Center approved the study protocols for all examination cycles, and participants signed informed consents at each study visit.

Participants attended a routine Framingham Heart Study clinical visit every four to eight years. Blood pressure was measured at rest twice using a mercury column sphygmomanometer. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Clinically significant heart murmur was diagnosed by the presence of a grade three or more out of six systolic murmur, or any diastolic murmur, as determined during standardized examination at the Heart Study. Hypertension treatment was ascertained by self-report of medications. Diabetes was defined as fasting serum glucose ≥ 126 mg/dl, history of physician-diagnosed diabetes or use of medications for diabetes. Heart failure was adjudicated incorporating Framingham clinic and outside medical records on the basis of major and minor clinical criteria as described previously.⁸

Fasting blood samples were collected at each examination. Standardized insulin levels were measured in plasma as immunoreactive insulin. Insulin resistance was defined as the top quartile of the previously validated homeostasis model assessment of insulin resistance (HOMA-IR), assessed by the formula = (fasting plasma insulin [microunits per milliliter]) X (fasting plasma glucose [millimoles per liter])/22.5.⁹ Fasting plasma insulin was measured with different assays at the 2 examinations. At examination 5, we used EDTA plasma as total immunoreactive insulin and calibrated to serum levels for reporting purposes. Cross-reactivity of this assay with proinsulin at mid curve is approximately 40%; the intra-assay and interassay CVs ranged from 5.0% to 10.0%. At exam 7, the insulin level was specific, having essentially no cross-reactivity to insulin split-products (Linco Research, Inc., St. Charles, MO). Assay coefficient of variation was $<10\%$ on examination cycle 5 and $<6.8\%$ on examination cycle 7.^{10,11}

Identification of AF was made based on records collected from participants' Framingham examinations (interim cardiovascular events were routinely ascertained by Heart Study physicians), outside office visits and hospitalizations.¹² For Framingham Offspring participants, biennial health history updates included a routine question on AF. Participants were determined as having AF if an electrocardiogram showed either atrial fibrillation or atrial flutter. Incident AF cases underwent review by one of two Framingham cardiologists (DL or EJB).

Descriptive statistics were examined including percentages for discrete variables and mean and standard deviations for continuous variables. Insulin resistance was analyzed as a dichotomous variable defined as the upper quartile of HOMA-IR (yes/no). We assessed HOMA-IR and clinical risk factors for AF at examination 5 and followed participants for development of incident AF for up to 10 years or their 7th examination. We redefined the baseline characteristics at examination cycle 7, excluded individuals with interim AF and followed forward for the development of incident AF for up to 10 years. Multivariable-adjusted hazard ratios (HR) were estimated using Cox modeling to examine the relation between insulin resistance and AF up to 10 years of follow-up after confirming proportionality of hazards. Hazard ratios in the first model were adjusted for age and sex. In addition to age and sex, the second model was further adjusted for systolic blood pressure, hypertension treatment, PR interval, significant heart murmur, and heart failure – all established clinical risk factors for AF, as described previously.¹³ The third model had the same covariates as the second model plus body mass index. We determined the primary analysis had 80% power to identify an association between insulin resistance and new-onset AF at a HR of 1.41 with an alpha level of 0.05. All analyses were generated using SAS software, Version 9.1 (SAS Institute Inc. Cary, NC, USA). A two-sided $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the 4,583 person examinations representing 3,023 unique individuals (55% women; mean age 59 years) are described in Table 1. A total of 279 participants developed AF over 10 years follow-up including 64 with and 215 without insulin resistance at baseline (7,661 person-years follow-up with insulin resistance versus 27,426 person-years follow-up without insulin resistance).

We examined the association of insulin resistance with incident AF, adjusting for established AF risk factors in multivariable Cox proportional hazard models (Table 2). Insulin resistance was not associated with AF in age- and sex-adjusted models (hazard ratio [HR] 1.27, 95% confidence interval (CI) 0.92 to 1.76, $p = 0.15$), or in models adjusting for established AF risk factors regardless of whether body mass index was included or not. The cumulative incidence of AF according to presence versus absence of insulin resistance is shown on figure 1.

To further explore the relation of insulin resistance to AF, we performed an unadjusted association between insulin resistance and AF and no statistically significant association was identified (HR 1.10, 95% CI 0.83 to 1.45, $p = 0.52$). Unadjusted analysis relating the top quartile of HOMA-IR to the first quartile of HOMA-IR was not statistically significant (HR 1.12, 95% CI 0.80 to 1.56, $p = 0.50$).

Discussion

Previous studies have demonstrated an association between type 2 diabetes and metabolic syndrome with incident AF, suggesting that insulin resistance may be involved in the

pathogenesis of this arrhythmia.^{14–18} However, in our large, prospective, middle-aged to elderly community-based cohort we did not observe an association between insulin resistance and incident AF in unadjusted and multivariable-adjusted models.

Several potential factors may explain the lack of association between insulin resistance and incident AF in our study. Insulin resistance syndrome is clinically defined as the presence of high blood pressure, fasting blood sugar ≥ 100 mg/dL, large waist circumference, low HDL and high triglycerides. The clinical factors incorporated in metabolic syndrome may need to act in concert in order to predispose to AF, as shown on figure 2. In this scenario, insulin resistance would be a mediator between metabolic syndrome and AF. Alternatively, the correlations among known AF risk factors and insulin resistance may obscure the individual contributions of specific risk factors to incident AF. However, the correlation among hypertension, body mass index, fasting glucose and insulin resistance is an unlikely explanation of our negative results, because we observed no significant association in unadjusted models. Another possible explanation is that our study sample had a mean age of 59 years and had only a modest prevalence of cardiovascular risk factors. Having excluded 624 individuals with diabetes, only 23% of our study sample had hypertension and only 25% were obese (body mass index ≥ 30 kg/m²). We cannot rule out the possibility that an older, more ethnically diverse sample with a higher burden of cardiovascular risk factors may manifest an association between insulin resistance and incident AF. Potentially a larger sample size would have detected a more modest association between insulin resistance and incident AF. In addition, we did not use a hyperinsulinemic euglycemic clamp study, which may have resulted in some misclassification of insulin resistance; however, euglycemic clamp testing is impractical in large community-based epidemiologic studies.¹⁹ Finally, there may be a true lack of association between insulin resistance and new-onset AF.

Strengths of the present study include the prospective design, long-term follow-up, and rigorous ascertainment of AF cases. The study has potential limitations that merit discussion. Our study is community-based, participants were predominately middle-aged to elderly and were largely of European descent, with up to 10 years follow up. The generalizability of our findings to studies with longer follow up, a higher burden of comorbidities, other ages, and ethnicities/races is uncertain. In summary, in our large community-based sample we did not observe a significant association between insulin resistance and incident AF.

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References

1. Lempiäinen P, Mykkänen L, Pyörälä K, Laakso M, Kuusisto J. Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. *Circulation*. 1999; 100:123–128. [PubMed: 10402440]
2. Jeppesen J, Hansen TW, Rasmussen S, Ibsen H, Torp-Pedersen C, Madsbad S. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease: a population-based study. *J Am Coll Cardiol*. 2007; 49:2112–2119. [PubMed: 17531661]
3. Nichols GA, Reinier K, Chugh SS. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. *Diabetes Care*. 2009; 32:1851–1856. [PubMed: 19794003]
4. Hanley AJG. Prediction of Type 2 Diabetes Mellitus With Alternative Definitions of the Metabolic Syndrome: The Insulin Resistance Atherosclerosis Study. *Circulation*. 2005; 112:3713–3721. [PubMed: 16344402]
5. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. *Circulation*. 1995; 92:835–841. [PubMed: 7641364]
6. Lip GY, Varughese GI. Diabetes mellitus and atrial fibrillation: perspectives on epidemiological and pathophysiological links. *Int J Cardiol*. 2005; 105:319–321. [PubMed: 16274776]
7. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. *Prev Med*. 1975; 4:518–525. [PubMed: 1208363]
8. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*. 1993; 88:107–115. [PubMed: 8319323]
9. Kanauchi M. A new index of insulin sensitivity obtained from the oral glucose tolerance test applicable to advanced type 2 diabetes. *Diabetes Care*. 2002; 25:1891–1892. [PubMed: 12351505]
10. Meigs JB, Mittleman MA, Nathan DM, Tofler GH, Singer DE, Murphy-Sheehy PM, Lipinska I, D'Agostino RB, Wilson PW. Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. *JAMA*. 2000; 283:221–228. [PubMed: 10634338]
11. Meigs JB, Dupuis J, Herbert AG, Liu C, Wilson PW, Cupples LA. The insulin gene variable number tandem repeat and risk of type 2 diabetes in a population-based sample of families and unrelated men and women. *J Clin Endocrinol Metab*. 2005; 90:1137–1143. [PubMed: 15562019]
12. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994; 271:840–844. [PubMed: 8114238]
13. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasan RS, Benjamin EJ. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009; 373:739–745. [PubMed: 19249635]
14. Dagres N, Anastasiou-Nana M. Atrial fibrillation and obesity an association of increasing importance. *J Am Coll Cardiol*. 2010; 55:2328–2329. [PubMed: 20488303]
15. Dublin S, Glazer NL, Smith NL, Psaty BM, Lumley T, Wiggins KL, Page RL, Heckbert SR. Diabetes Mellitus, Glycemic Control, and Risk of Atrial Fibrillation. *J GEN INTERN MED*. 2010; 25:853–858. [PubMed: 20405332]
16. Korantzopoulos P, Kokkoris S, Papaioannides D. The Association of Metabolic Syndrome with Atrial Fibrillation: An Emerging Epidemiological and Pathophysiological Hypothesis. *Cardiology*. 2005; 104:148–149. [PubMed: 16118494]
17. Liu T, Li G. Inflammation: another potential mechanism between diabetes mellitus and atrial fibrillation. *Am J Cardiol*. 2008; 101:1681–1682. [PubMed: 18489956]
18. Mph AMCP, Mph SKAM, Md MA, Mph ARFM, Phd AAM. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. *American Heart Journal*. 2010; 159:850–856. [PubMed: 20435195]
19. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979; 237:E214–223. [PubMed: 382871]

Insulin Resistance	1094	1064	1030	865	285
No insulin resistance	3489	3414	3321	3043	1999

Figure 1.
The figure shows the cumulative incidence of AF according to presence (dark blue) versus absence (light blue) of insulin resistance, defined in the text as the highest quartile of the homeostasis model assessment of insulin resistance.⁹

Figure 2.
Directed acyclic graphs showing examples of causal inference about the relation between insulin resistance and atrial fibrillation.

Table 1

Baseline Participant Characteristics

Characteristic	N=3023
Age (years)	59.2±6.9
Women	54.8%
Body mass index (kg/m ²)	27.4±4.7
Systolic blood pressure (mm Hg)	127±18
Fasting glucose (mg/dL)	96±10
Hypertension treatment	22.7%
Electrocardiographic PR interval (msec)	164±24
Significant precordial heart murmur	1.7%
Prevalent heart failure	0.4%
HOMA-IR [†] (mg/dL)	6.1±3.3

mean ± SD for continuous variables and percentages for dichotomous variables.

[†] homeostasis model assessment of insulin resistance

Table 2

Results from multivariable-adjusted proportional hazards regression models.

Model	HR	95% CI	p value
1 [*]	1.27	0.92—1.76	0.15
2 [†]	1.18	0.84—1.65	0.34
3 [‡]	1.03	0.72—1.46	0.89

* Adjusted for age and sex

† Adjusted for Model 1 and systolic blood pressure, treatment for hypertension, electrocardiographic PR interval, heart murmur and heart failure

‡ Adjusted for Model 2 and BMI