Insulin Sensitivity and the Risk of Incident Hypertension

Insights from the Insulin Resistance Atherosclerosis Study

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OBJECTIVE — The insulin resistance syndrome has been described as including hypertension. Previous studies have documented cross-sectional associations between insulin sensitivity (S_I) and blood pressure or prevalent hypertension. Prospective data have been sparse.

RESEARCH DESIGN AND METHODS — The Insulin Resistance Atherosclerosis Study (IRAS) is a prospective study of the associations of S_I with atherosclerosis and other risk factors for cardiovascular disease. We examined the association between S_I, measured using the frequently sampled intravenous glucose tolerance test with minimal model analysis, and incident hypertension (defined as per the Joint National Committee), at the 5-year examination in 840 IRAS participants who were free of hypertension at the baseline examination.

RESULTS — Adjusted for age, sex, ethnicity, and smoking status, for each unit greater S_I, the risk of hypertension was 10% lower (95% CI 2–19, $P < 0.05$).

CONCLUSIONS — These findings, from a prospective study, support the presence of a modest protective association between greater S_I and lower risk of hypertension. These findings support the contention that interventions that improve S_I may be beneficial with respect to the development of hypertension and cardiovascular disease. This contention should be tested in randomized clinical trials.

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Hyperinsulinemia has been associated with cardiovascular risk factors, including high triglyceride concentrations, low HDL cholesterol concentrations, high blood pressure, and obesity (1). Surprisingly, there has been debate regarding the role of insulin resistance in the regulation of blood pressure. Haffner (2,3) commented on the conflicting evidence in several reports and Reaven (4) suggested that "insulin resistance may or may not play a role in blood pressure regulation." In the intervening period, insulin sensitivity (S_I) has been linked to a variety of aspects of blood pressure regulation, including salt sensitivity and the failure to observe the expected nocturnal fall in blood pressure (5), the response of blood pressure to exercise (6), and left ventricular mass (7). On the other hand, insulin has been shown to lack a direct pressor effect (8) and S_I has not been associated consistently with blood pressure or hypertension status (9,10).

Given the current uncertainty regarding the nature of the association between S_I and blood pressure regulation, we sought to address the following question in a prospective cohort study: Is S_I associated with the risk of developing incident hypertension independent of age, gender, and ethnicity?

RESEARCH DESIGN AND METHODS

Design and population

The objectives, design, and methods of The Insulin Resistance Atherosclerosis Study (IRAS) have been published previously (11). Briefly, the major objective of IRAS was to assess the relationship between insulin resistance and atherosclerosis. This cross-sectional epidemiologic study was conducted at four clinical centers. African Americans and non-Hispanic whites were studied in centers in Oakland and Los Angeles, California, and Hispanics and non-Hispanic whites were studied in centers in San Luis Valley, Colorado, and San Antonio, Texas. In Los Angeles and Oakland, participants were recruited from members of a nonprofit health maintenance organization. In Colorado and Texas, participants were recruited from ongoing population-based epidemiologic studies of the risk factors for type 2 diabetes and coronary heart disease in Hispanics and non-Hispanic whites, the San Luis Valley Diabetes Study (12) and the San Antonio Heart Study (13), respectively. Sampling strategies were used to identify sufficient numbers of persons in different ethnic, age, gender, and glucose tolerance groups to allow an efficient study of relationships among and within these groups. Persons taking insulin were excluded. IRAS was approved by the institutional review boards of all four clinical centers and the coordinating center, and informed consent was obtained for all participants.

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Abbreviations: ACEI, ACE inhibitor; ARIC, Atherosclerosis Risk in Communities; CARDIA, Coronary Artery Risk Development in (Young) Adults; FSIGT, frequently sampled intravenous glucose tolerance test; IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study; MINMOD, minimal model; NGT, normal glucose tolerance; S_I, insulin sensitivity;

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of normotensive participants by follow-up status*

Characteristic	Lost to Follow-up	Re-examined	*P*
Age (years)	55 ± 9	54 ± 9	0.19
Gender			0.48
Men	68 (42.2)	380 (45.2)	
Women	93 (57.8)	460 (54.8)	
Ethnicity			0.42
African Americans	33 (20.5)	204 (24.3)	
Hispanics	65 (40.4)	298 (35.5)	
Non-Hispanic whites	63 (39.1)	338 (40.2)	
Cigarette smoking status			0.001
Current	46 (28.9)	137 (16.3)	
Past	51 (32.1)	332 (39.6)	
Never	62 (39.0)	370 (44.1)	
Glucose tolerance status			0.08
Diabetes	52 (32.3)	201 (23.9)	
Impaired	33 (20.5)	182 (21.7)	
Normal	76 (47.2)	457 (54.4)	
S_I	1.89 ± 2.13	2.04 ± 2.13	0.46

Data are means ± SD or *n* (%).

Baseline clinic examination

The IRAS baseline clinical examination consisted of two 4-h visits scheduled ~1 week apart (14). Before each visit, participants were asked to refrain from alcohol and heavy exercise for 24 h, from food for 12 h, and from smoking on the day of the examination. The first visit included a 75-g oral glucose tolerance test; blood was collected for fasting and 2-h glucose samples. Glucose tolerance status was classified according to World Health Organization criteria as either normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetes (15). Race and ethnicity were self-reported. Cigarette smoking status was assessed by self-report as current, past, or never.

Blood pressure was measured three times using a mercury manometer at each visit as part of the baseline examination. The average of the last two measurements for each visit was used to characterize the blood pressure for each visit. The average of the blood pressure measurements for the two visits was used to classify individuals with respect to hypertension status. Hypertension was defined based on a systolic blood pressure of at least 140 mmHg, a diastolic blood pressure of at least 90 mmHg, or pharmaceutical treatment for hypertension.

S_I was assessed by the frequently sampled intravenous glucose tolerance test (FSIGT) with minimal model (MINMOD) analyses. The protocol has been previously described in detail (11,14). The FSIGT (insulin-modified with 12 time points) protocol used in the IRAS study has been compared to the hyperinsulinemic-euglycemic clamp and shown to be a valid measure of insulin resistance with a correlation of ~0.6 with measures from the clamp, albeit with values ~50% lower than clamp values when expressed in the same units (16). S_I is expressed in the following units: $10^{-4} \times \text{min}^{-1} \times \mu\text{U}^{-1} \times \text{ml}^{-1}$.

Plasma glucose was measured with the glucose oxidase technique on an automated autoanalyzer (Yellow Springs Equipment). Insulin was measured using the dextran-charcoal radioimmunoassay, which has considerable cross-reactivity with proinsulin.

Follow-up clinic examination

Participants were recruited to return for a follow-up examination after ~5 years from the date of the baseline clinic examination. Many of the measures obtained at baseline were repeated at that time. Hypertension status was determined using the same procedures as were used at baseline.

Statistical analysis

Descriptive summary statistics were generated for the study population using means (and SEs) for continuous variables and proportions for dichotomous variables. The associations between baseline characteristics and incidence of hypertension were examined in unadjusted analyses using *t* tests (for continuous variables) and cross-tabulations with χ^2 tests (for dichotomous variables) and in adjusted analyses using logistic regression analysis. First, the association of S_I and incident hypertension was modeled using logistic regression in an unadjusted model and in a model including potential confounders: age, gender, ethnicity-clinic, and smoking status. The model adjusted for potential confounders was deemed to be the appropriate test of whether S_I was associated independently with risk of incident hypertension. We did not adjust for baseline blood pressure values. Such an adjustment could represent overadjustment for insulin resistance. If insulin resistance is associated with blood pressure levels, then baseline blood pressure levels would be dependent on baseline measures of insulin resistance. Hence, adjustment for baseline blood pressure levels would represent adjustment for baseline insulin resistance. In addition, we did not adjust for glucose tolerance status for two reasons. First, because insulin resistance contributes to the development of diabetes, adjustment for glucose tolerance status could represent overadjustment for a variable on the causal pathway between insulin resistance and hypertension (17,18). Second, because the hyperglycemia related to diabetes can lead to worsened insulin resistance through glucose toxicity, adjustment for glucose tolerance status might also represent overadjustment for a causal antecedent. Similarly, we did not adjust for adiposity, as greater adiposity may cause worsened S_I, and therefore also act as a causal antecedent.

RESULTS

— The IRAS population comprised 1,624 individuals at baseline, including 840 participants who were free of hypertension at baseline and reexamined at 5 years. There were no interim examinations. A total of 602 (37.1%) had hypertension at baseline, 21 (1.3%) had died, and 161 (9.9%) were free of hypertension at baseline but not reexamined. The baseline characteristics of those reexamined (840) and those not reexamined (161) are shown in Table 1. Persons lost to follow-up were more likely to be cigarette smokers at baseline ($P < 0.001$) and somewhat more likely to have diabetes

Table 2—*5-year risk of incident hypertension by baseline characteristics*

Characteristic	Baseline (*n*)	Incident hypertension	Risk (%)	*P*
Total population	840	202	24.0	
Age				0.13
39–54 years	455	100	22.0	
55–69 years	385	102	26.5	
Sex				0.22
Men	380	99	26.0	
Women	460	103	22.4	
Ethnicity				0.001
African Americans	204	71	34.8	
Hispanics	298	56	18.8	
Non-Hispanic whites	338	75	22.2	
Cigarette smoking status				0.17
Current	137	32	23.4	
Past	332	91	27.4	
Never	370	79	21.4	
S_I				0.007
<1.44 (median)	384	107	27.9	
≥1.44 (median)	388	76	19.6	

($P = 0.08$). There were no substantial differences with respect to age, gender, ethnicity, or S_I.

At the 5-year follow-up examination, 202 (24.0%) participants had developed hypertension, including 112 (13.3%) who were taking blood pressure–lowering medications and 90 (10.7%) who were untreated. The risk of incident hypertension is shown according to baseline characteristics in Table 2. African Americans were more likely to develop hypertension than either Hispanics or non-Hispanic whites. Persons with greater S_I were at lower risk of developing hypertension. Risk of incident hypertension was not associated with age, gender, or cigarette smoking status in unadjusted analyses.

The odds ratios (and corresponding 95% CIs) for the development of hypertension per unit of S_I are shown in Table 3. In an unadjusted analysis, the risk of developing incident hypertension was 11% lower for every one unit greater S_I ($P < 0.05$). Adjustment for the potentially confounding effects of age, gender, ethnicity, and cigarette smoking did not influence the strength of this association. Results did not differ importantly by diabetes status (P for interaction = 0.62). Due to the complexity of interpretation of a 1-unit difference in S_I, we also examined the difference in incidence of hypertension across quartiles of S_I. This effect corresponds to a 33% (95% CI −8 to 52) lower risk of developing hypertension for the most sensitive quartile of S_I in comparison with the least sensitive quartile (Fig. 1). The third quartile of S_I had a 53% (95% CI 12–71) lower risk of developing hypertension in comparison with the least sensitive quartile (Fig. 1). Whether this apparent departure from a linear relationship represents random variation or a true plateau is not clear. The strength of the association between S_I and incidence of hypertension did not differ according to ethnicity (P for interaction = 0.35). In the multivariable-adjusted model (full results shown in Table 4), the risk of incident hypertension was decreased in persons with greater S_I, and increased in persons of African-American ethnicity. There was a trend toward increased risk of incident hypertension at older ages.

CONCLUSIONS — These findings support the presence of a modest protective association between S_I and risk of incident hypertension, independent of age, gender, and ethnicity. These results are the first reported from a prospective study linking a direct measure of S_I to the risk of incident hypertension. Previously, insulin concentrations have been linked to incidence of hypertension in several prospective studies (19–21); however, it is important to note that hyperinsulinemia is not equivalent to insulin resistance, inasmuch as insulinemia is influenced by insulin secretion as well as by insulin resistance. The strength of the association between S_I and incidence of hypertension was similar across ethnic groups. This latter finding conflicts somewhat with the results reported from the Atherosclerosis Risk in Communities (ARIC) Study (19) and the Coronary Artery Risk Development in (Young) Adults (CARDIA) Study (20). In the ARIC and CARDIA studies, the association between fasting serum insulin concentration, a measure of hyperinsulinemia, and incidence of hypertension was weaker in African Americans than in whites. It is important to note that the sample size available for the current analysis was much smaller than that included in the ARIC and CARDIA reports; hence, much less power was available to examine ethnic differences. Additional research using direct measures of insulin resistance could help clarify this issue.

Although not the primary focus of this report, these findings are consistent with previous reports indicating a greater risk of development of hypertension in African Americans in comparison to

Table 3—*Odds ratios for the 5-year risk of incident hypertension associated with 1 unit of S_I*

Model	Total population	Diabetes	Nondiabetic
n	770	182	588
S_I			
Unadjusted	0.89 (0.81–0.98) $P = 0.019$	0.88 (0.58–1.35)	0.95 (0.86–1.05)
Adjusted for age, gender, ethnicity-clinic, smoking	0.90 (0.81–0.99) $P = 0.024$	0.87 (0.56–1.37)	0.92 (0.83–1.03)

Data are odds ratio (95% CI).

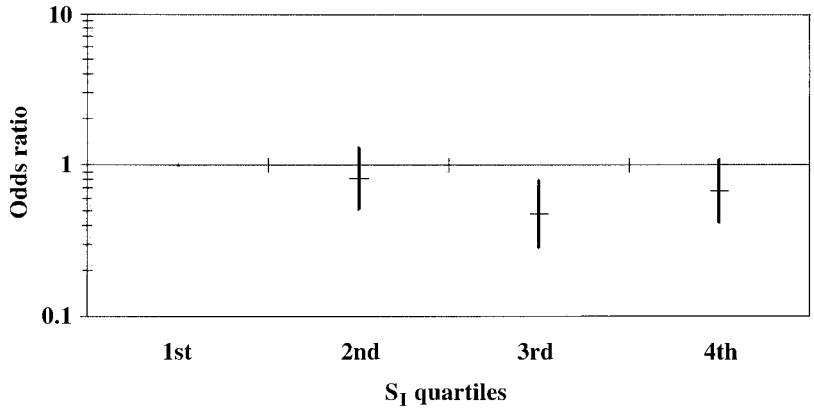

Figure 1—*Odds ratios and corresponding 95% CIs for risk of developing incident hypertension by quartile S_I. The least-sensitive quartile was the referent group. Means (and ranges) of S_I ($10^{-4} \times min^{-1} \times \mu U^{-1} \times ml^{-1}$) by quartile follow: quartile 1: 0.22 (0–0.065); quartile 2: 1.04 (0.66–1.44); quartile 3: 2.06 (1.46–2.90); quartile 4: 4.84 (2.91–19.4).*

whites (20) and a similar risk of development of hypertension in Hispanics and non-Hispanic whites (22,23).

This study has several limitations. The insulin-modified FSIGT was chosen for use in IRAS based on a determination that the results had sufficient validity and the test was logistically feasible for use in large-scale population studies (16). At the time that IRAS was initiated, there were substantial concerns regarding the logistical feasibility of conducting hyperinsulinemic-euglycemic clamps in large-scale population studies. The measure of S_I from the FSIGT was found to have a correlation of 0.6 with results from the clamp (16). The likely effect of the increased measurement error related to using the FSIGT method rather than the clamp would be to introduce misclassification of exposure (insulin resistance) that was nondifferential with respect to the outcome (incident hypertension). The corresponding bias would be toward a null finding; hence, the observed association reported here is likely an underestimate of the true strength of the association between insulin resistance and incident hypertension. The FSIGT method produces S_I values indistinguishable from zero in a large proportion of persons with diabetes (16). Recognizing the measurement error inherent in any measurement of insulin resistance and in the FSIGT specifically, individuals whose S_I is estimated as equal to zero are very insulin resistant. We included the categorical analysis of the relationship between S_I and incident hypertension partly to address this issue by reducing the impact of these individuals on the results of the regression. All participants with S_I values of zero were included in the least-sensitive quartile.

Furthermore, the study population was not population based. The use of a population-based sample would provide greater support for generalizability; however, this apparent limitation could also be considered a strength for this analysis. Since the major interest was to detect an association between S_I and hypertension, the over-representation of persons with impaired glucose tolerance and diabetes may have improved the power to detect this association by increasing the inclusion of persons with insulin resistance. Likewise, the over-representation of African Americans and Hispanics could be considered to be a strength. Finally, the reexamination rate was 83.9%. Losses to follow-up reduced the power of these analyses and may have biased our results if the determinants of incident hypertension differed by follow-up status.

This study also has several strengths. The prospective design of this study enabled us to avoid limitations inherent in cross-sectional studies regarding the temporality of the association and the impact of antihypertensive medications on S_I. Hypertension status was defined based on exacting criteria and sound methodology. S_I was assessed using a validated and accepted method. Other covariates were also assessed using accepted methodology. These aspects of study design and conduct strengthen the inferences that can be drawn from these findings.

These findings provide strong evidence that insulin resistance increases the risk of hypertension and are consistent with the body of literature linking insulin resistance to blood pressure regulation (5–7). These findings have several important implications. From a clinical perspective, the routine measurement of S_I is not supported by the modest association observed in this study. The FSIGT employed in IRAS is labor intensive and imposes a significant burden on the participant, requiring establishment of intravenous access in both arms and several hours of time. On the other hand, these findings support the contention that interventions that improve S_I may help prevent the development of hypertension and cardiovascular disease. Physical activity and a healthy dietary intake pattern are two interventions that favorably influence S_I (24). Several pharmacologic agents, including ACE inhibitors (ACEIs), have been shown to have favorable effects on S_I (25,26). Recently in the Heart Outcomes Prevention Evaluation (HOPE)

Table 4—*Multivariable-adjusted odds ratios for the 5-year risk of incident hypertension*

Variable	Odds ratio	Lower 95% confidence limit	Upper 95% confidence limit	*P*
Age (/5 years)	1.10	1.00	1.22	0.06
Gender (men/women)	1.09	0.77	1.55	0.62
Ethnicity				0.01
African Americans/non-Hispanic whites	1.55	1.02	2.36	0.04
Hispanics/non-Hispanic whites	0.77	0.51	1.16	0.21
Smoking				0.31
Current/never	1.18	0.71	1.95	0.53
Past/never	1.35	0.92	1.97	0.13
S_I	0.90	0.81	0.99	0.02

Trial, the ACEI ramipril was shown to reduce cardiovascular disease morbidity and mortality and the incidence of type 2 diabetes (27,28). The current findings provide evidence to support the speculation that the beneficial effects of physical activity, a healthy dietary intake pattern, and ACEIs on risk of cardiovascular disease might be mediated, at least in part, through their effects on insulin sensitivity and blood pressure. Other pharmacologic and nonpharmacologic approaches to influencing this mechanism should be examined in randomized clinical trials.

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