Risk Factors for Progression to Incident Hyperinsulinemia: The Atherosclerosis Risk in Communities Study, 1987–1998

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Hyperinsulinemia is a marker of insulin resistance, a correlate of the metabolic syndrome, and an established precursor of type 2 diabetes. This US study investigated the role of risk factors associated with hyperinsulinemia in cross-sectional studies in progression to incident hyperinsulinemia. Nondiabetic participants from the Atherosclerosis Risk in Communities Study (n = 9,020) were followed from 1987 to 1998 for the development of hyperinsulinemia (fasting serum insulin ≥90th percentile, 19.1 µU/ml). After adjustment for demographic characteristics, all risk factors simultaneously, and baseline insulin value, the risk of progressing to hyperinsulinemia increased per standard deviation increase in baseline uric acid (odds ratio (OR) = 1.3, 95% confidence interval (CI): 1.2, 1.4; per 1.4 mg/dl) and waist/hip ratio (OR = 1.4, 95% CI: 1.2, 1.5; per 0.08) and was inversely associated with high density lipoprotein cholesterol (OR = 0.8, 95% CI: 0.7, 0.9; per 0.4 mmol/liter). Starting to smoke (OR = 1.5, 95% CI: 1.2, 2.0) and becoming obese (OR = 2.4, 95% CI: 1.8, 3.1) during the study were also associated with increased risk. The associations were similar across race and gender groups. These data suggest that, in addition to weight gain, hyperuricemia, dyslipidemia, and smoking can be detected prior to development of hyperinsulinemia.

diabetes, non-insulin-dependent; hyperinsulinemia; insulin resistance; longitudinal studies; metabolic syndrome X; risk factors

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein.

A high concentration of circulating insulin—hyperinsulinemia—may represent a defect in insulin metabolism or a compensatory response to insulin resistance. In either case, hyperinsulinemia is correlated with insulin resistance in persons without diabetes (1, 2) and has been used extensively as a surrogate for insulin resistance in epidemiologic studies. Insulin resistance is thought to be a precursor of the metabolic syndrome (3), a clustering of lipid and nonlipid risk factors for coronary heart disease (4).

Longitudinal studies have identified concurrent increases in insulin concentrations and overall and abdominal obesity (5, 6). Cross-sectional studies have demonstrated that hyperinsulinemia is correlated with a clustering of metabolic syndrome components such as high blood pressure, diabetes, hyperuricemia, and dyslipidemia (7–10) as well as markers of inflammation (11). Furthermore, health behaviors such as physical inactivity (12) and cigarette smoking (13–16) have been correlated with hyperinsulinemia. However, with the exception of longitudinal studies relating obesity and the development of hyperinsulinemia, cross-sectional studies are unable to characterize the temporal association between metabolic risk factors and hyperinsulinemia.

Current thought postulates that obesity leads to the development of hyperinsulinemia and that metabolic syndrome...
risk factors develop thereafter. However, it is plausible that some metabolic risk factors or other coronary heart disease risk factors are present prior to the development of hyperinsulinemia. We tested the hypothesis that previously identified correlates of hyperinsulinemia and insulin resistance predict progression to incident hyperinsulinemia in a population-based sample.

MATERIALS AND METHODS

Study population

The Atherosclerosis Risk in Communities (ARIC) cohort study is a longitudinal study of atherosclerotic disease. A probability sample of Blacks and Whites aged 45–64 years was recruited from the suburbs of Minneapolis, Minnesota; Forsyth County, North Carolina; Washington County, Maryland; and Jackson, Mississippi (Black residents only). Participants (n = 15,792) underwent a baseline examination in 1987–1989 and three follow-up examinations at approximately 3-year intervals through 1998. A detailed description of the study design and sampling methods has been published previously (17).

For this analysis, participants were excluded for the following reasons: self-reported race that was neither Black nor White or Black race and living in Minnesota or Maryland centers (small numbers; n = 103), failure to return for the final examination (n = 2,773), fasting for less than 8 hours before the baseline and final examinations (n = 872), and missing insulin measurements at either examination (n = 159). Because of the relation between diabetes and insulin abnormalities, participants with diabetes at baseline (n = 1,594) and participants who used oral agents to control diabetes during follow-up were excluded (n = 22). To estimate progression to incident hyperinsulinemia, we excluded participants whose fasting insulin levels were above the 90th percentile at baseline (20.1 μU/ml; n = 1,301). In analyses of baseline covariates and incident hyperinsulinemia, participants with prevalent coronary heart disease at baseline were excluded (n = 446); 8,574 participants were included in the analysis. To investigate changes in covariates and hyperinsulinemia, participants who developed coronary heart disease over follow-up were excluded (n = 1,022); 7,998 participants were included in the analyses.

Data collection

Fasting (≥8 hours) blood samples were drawn from an antecubital vein and were processed immediately. Serum and plasma were frozen at −70°C and were assayed at a central laboratory. At baseline, serum insulin was measured by radioimmunoassay (Cambridge Medical Diagnosis, Inc., Billerica, Massachusetts). However, the method used for insulin measurement at baseline was no longer available at the final examination, when it was measured with an enzyme-linked immunosorbent assay (Boehringer Mannheim Corporation, Mannheim, Germany). Participants with insulin values above the 90th percentile at the final examination, 19.08 μU/ml, were defined as having incident hyperinsulinemia.

Demographic and lifestyle characteristics were assessed at baseline from home interviews, during which standardized questionnaires were used (18). Dietary intake was assessed by using a modified version of the 61-item food frequency questionnaire developed by Willett et al. (19). Smoking and alcohol drinking status were reported. The Baecke questionnaire (20) was used to assess leisure-time physical activity (e.g., gardening) and sports-related physical activity (e.g., jogging) on a scale from 1 (low) to 5 (high). Medication use was identified and defined by coding all reported medications, vitamins, and supplements used in the 2 weeks prior to the clinic examination.

Weight to the nearest pound (1 pound = 0.454 kg) and height to the nearest centimeter were measured. Body mass index (BMI) was calculated as the ratio of weight (kilograms) to standing height (meters) squared (kg/m²). Participants with a BMI of ≥30 were classified as obese. Waist girth was measured at the umbilicus, and hip girth was measured as the largest diameter around the gluteal muscles.

Total cholesterol (21) and triglycerides (22) were measured in plasma with enzymatic methods, and low density lipoprotein (LDL) cholesterol was calculated (23). High density lipoprotein (HDL) cholesterol was determined after dextran-magnesium precipitation (24). Apolipoprotein B was measured by radioimmunoassay (25). Fibrinogen was determined by the thrombin time titration method (26) using reagents obtained from General Diagnostics (Organon Teknika, Morris Plains, New Jersey). Specific measurement techniques have already been published (27). Factor VII and VIII levels were measured by using coagulation tests (George King Biomedical, Overland Park, Kansas) (28). Uric acid was calculated according to standard methods described by Haeckel (29) and published in the ARIC Study (30).

Blood pressure was measured from seated participants three times by using a random zero sphygmomanometer. The average of the last two measurements is reported here. Hypertension was defined as systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or use of medications to lower blood pressure in the 2 weeks prior to the clinic examination. Serum glucose was calculated by using a hexokinase/glucose-6-phosphate dehydrogenase method on a Coulter DACOS device (Coulter Corporation, Miami, Florida). Diabetes was defined as a fasting serum glucose level of ≥126 mg/dl (7 mmol/liter), a nonfasting glucose level of ≥200 mg/dl (11.1 mmol/liter), self-reported use of medications for diabetes, or a self-reported previous physician diagnosis of diabetes. Prevalent coronary heart disease was defined as a history of coronary artery bypass surgery, balloon angioplasty, or myocardial infarction based on electrocardiograph or physician diagnosis.

Menopausal status was ascertained by self-report at each examination and was classified according to the frequency of menstrual periods in the 2 years prior to each examination. Women reporting regular menstrual periods were categorized as premenopausal; women with irregular, but still present, menstrual periods were classified as perimenopausal. Women who ceased menstrual periods naturally, underwent bilateral oophorectomy, or were currently using hormone replacement therapy were considered postmeno-
pausal. At each examination, women were asked whether they had used prescription oral hormone replacement therapies (estrogen or estrogen plus progestin) during the previous examination interval. Women who reported hormone use at any time were compared with never users.

**Statistical methods**

The distribution of potential risk factors for hyperinsulinemia was calculated in the total sample and was stratified by incident hyperinsulinemia. Means and proportions of risk factors were compared by hyperinsulinemia status using $t$ tests and $\chi^2$ tests, respectively. Changes in risk factors during the study were calculated as the simple difference between continuous risk factors measured at the baseline and final examinations (BMI; waist/hip ratio; total, LDL, and HDL cholesterol; triglycerides) or as changes in the prevalence of categorical variables (obesity, smoking, alcohol drinking, diabetes, coronary heart disease, hypertension, menopause, hormone replacement therapy use).

**Measurement error correction.** Intraindividual variability in laboratory measurements was estimated from repeated measurements taken 1–2 weeks apart. Reliability coefficients, interpreted as the correlation between measures at repeat visits, were calculated from a nested random-effects model as the proportion of variance between persons divided by the total proportion of variance (within-person and method error). The following reliability coefficients in the ARIC Study have been published: baseline insulin = 0.88, uric acid = 0.91, glucose = 0.84 (31); BMI = 0.95, waist/hip ratio = 0.94 (32); total and HDL cholesterol each = 0.94, triglycerides and LDL cholesterol each = 0.85 (33); fibrinogen = 0.72, factor VII = 0.78, factor VIII = 0.86 (34). The unpublished repeatability coefficient for insulin at the final examination was 0.77, and estimates for systolic and diastolic blood pressure were 0.75 and 0.65, respectively. Estimates were not available for white blood cell count.

The term “measurement error” is used to encompass all short-term within-person variability (due to biologic variability or measurement) of a factor. Large measurement error in any of the model’s independent variables highly associated with the outcome could greatly bias the usual estimates of coefficients of other correlated variables in the model. This possibility is of greatest concern for baseline insulin, which obviously could be highly associated with crossing an insulin cutoffpoint to hyperinsulinemia status. Thus, all models were corrected for measurement error in baseline insulin by using a regression calibration method (35). Observed values of independent variables for which measurement error correction was implemented were transformed to expected values conditional on the observed values of all other variables in the model, that is, conditional Stein estimators (36). Comparisons were made with models with no correction at all for measurement error and after additional correction for measurement error in the other baseline continuous variables.

**Multivariable regression modeling.** Logistic regression was used to estimate odds ratios and 95 percent confidence intervals of hyperinsulinemia by baseline risk factors and changes in risk factors during the study. First, we investigated the shape of the association between each continuous risk factor of interest and incident hyperinsulinemia by categorizing risk factors into quintiles. Where assumptions of linearity were not violated, we calculated odds ratios for a one standard deviation increase in the risk factor; odds ratios for categorical risk factors were calculated on the basis of a referent level. We performed tests of heterogeneity of effect across race and gender groups by including multiplicative interaction terms in logistic regression models. The presence of interaction was determined by a significant change in the model maximum-likelihood chi-square value following removal of the term in nested models.

Two separate logistic regression analyses evaluating “minimal” and “multivariable” associations are presented here. The minimal logistic model adjusted for race, study center, gender, age, and baseline insulin, whereas the multivariable logistic model adjusted simultaneously for all risk factors by including terms for all noncollinear risk factors in the model along with terms in the minimal model. Most odds ratios were calculated from a multivariable model that included continuous BMI, and a separate model was used to calculate odds ratios for obesity. Separate multivariable models restricted to women were used to calculate odds ratios for menopause status and hormone replacement therapy use. All analyses were conducted by using the SAS software system, version 8.1 (SAS Institute, Inc., Cary, North Carolina).

**RESULTS**

**Baseline covariates**

At baseline, the mean age of the study population was 54 years, slightly more than half (57 percent) were women, and Black participants comprised 18 percent of the cohort (table 1). Participants who became hyperinsulinemic were, on average, more obese, with a larger waist/hip ratio, and were less likely to drink alcohol or engage in physical activity. In that group, baseline lipids were less favorable (lower HDL cholesterol and higher LDL cholesterol and triglycerides), inflammatory and hemostatic markers (factor VIII-C, factor VII, and fibrinogen) and uric acid levels were higher, and blood pressure and the prevalence of hypertension were higher. Among women, there was no difference in menopausal status, but a smaller proportion who used hormone replacement therapy at baseline developed hyperinsulinemia.

Participants were followed for an average of 8.9 years (standard deviation, 0.3). The risk of developing hyperinsulinemia was 5.4 times higher per standard deviation (8.16 $\mu$/ml) elevation in baseline insulin value (95 percent confidence interval: 4.7, 6.1) after adjustment for age, race, gender, and study center. In models minimally adjusted for race, study center, and baseline insulin, neither age (gender adjusted) nor gender (age adjusted) was associated with incident hyperinsulinemia (table 2). The risk of developing hyperinsulinemia increased monotonically by quintiles of BMI, waist/hip ratio, and uric acid and was inversely associated with HDL cholesterol (data not shown). Similarly, moderate elevations in the risk of hyperinsulinemia were
found with baseline obesity (BMI, waist/hip ratio, obesity prevalence), high uric acid concentrations, and smoking status. HDL cholesterol was inversely associated with incident hyperinsulinemia per standard deviation change. In multivariable models adjusting simultaneously for all noncollinear variables, only waist/hip ratio, uric acid, and smoking remained significantly positively associated with progression to hyperinsulinemia. HDL cholesterol, male gender, and triglycerides were inversely associated with the risk of developing hyperinsulinemia.

Changes in risk factors

On average, BMI, waist/hip ratio, and triglycerides increased during follow-up, while other lipid values decreased slightly (table 3). Associations between changes

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**TABLE 1. Baseline characteristics of the total sample and by incident hyperinsulinemia, Atherosclerosis Risk in Communities Study, 1987–1989**

| Characteristic                                      | Total sample (n = 8,574) | Incident hyperinsulinemia | p value* |
|-----------------------------------------------------|--------------------------|---------------------------|----------|
|                                                     | No (n = 7,725)           | Yes (n = 849)             |          |
| Age (years) (mean (SD†))                            | 53.7 (5.7)               | 53.5 (5.7)                | 0.5795   |
| Gender: % women                                      | 57.4                     | 57.7                      | 0.18     |
| Race: % Black                                        | 18.1                     | 17.0                      | <0.0001  |
| Highest level of education (%)                       |                          |                           | <0.0001  |
| <high school                                         | 16.5                     | 15.8                      | 23.1     |
| High school                                          | 43.1                     | 43.4                      | 40.5     |
| >high school                                         | 40.4                     | 40.8                      | 36.4     |
| Body mass index (mean (SD))                         | 26.6 (4.5)               | 26.3 (4.4)                | 29.4 (4.8) <0.0001 |
| Obese: % ≥30                                        | 19.5                     | 17.3                      | 40.1     <0.0001 |
| Waist/hip ratio (mean (SD))                         | 0.910 (0.077)            | 0.907 (0.077)             | 0.946 (0.067) <0.0001 |
| % of calories from carbohydrates (mean (SD))        | 48.9 (9.1)               | 49.0 (9.1)                | 48.7 (9.2) 0.3765 |
| Current cigarette smoking (%)                       | 25.3                     | 22.2                      | 23.2     0.4867 |
| Current alcohol drinking (%)                        | 61.7                     | 62.6                      | 54.1     <0.0001 |
| Sports-related physical activity§ (mean (SD))       | 2.50 (0.80)              | 2.52 (0.80)               | 2.37 (0.74) <0.0001 |
| Total cholesterol (mmol/liter) (mean (SD))          | 5.52 (1.03)              | 5.51 (1.02)               | 5.53 (1.10) 0.6730 |
| HDL† cholesterol (mmol/liter) (mean (SD))           | 1.40 (0.44)              | 1.41 (0.44)               | 1.24 (0.39) 0.001 |
| LDL† cholesterol (mmol/liter) (mean (SD))           | 3.51 (0.97)              | 3.50 (0.97)               | 3.60 (1.00) 0.0061 |
| Triglycerides (mmol/liter) (mean (SD))              | 1.33 (0.76)              | 1.31 (0.75)               | 1.52 (0.84) <0.0001 |
| Factor VIII-C (mean (SD))                           | 124.4 (33.5)             | 123.8 (33.3)              | 129.8 (35.4) <0.0001 |
| Factor VII (mean (SD))                              | 116.9 (27.0)             | 116.5 (26.6)              | 120.4 (30.7) <0.0001 |
| Fibrinogen (mg/dl) (mean (SD))                      | 293.0 (59.4)             | 291.8 (59.7)              | 303.3 (64.7) <0.0001 |
| White blood cell count (mean (SD))                  | 5.9 (1.8)                | 5.9 (1.8)                 | 6.1 (1.8) 0.0008 |
| Systolic blood pressure (mmHg) (mean (SD))          | 118.0 (16.7)             | 117.5 (16.6)              | 122.5 (17.5) <0.0001 |
| Diastolic blood pressure (mmHg) (mean (SD))         | 72.5 (10.5)              | 72.2 (10.4)               | 75.3 (10.5) <0.0001 |
| Hypertension (%)                                    | 25.9                     | 24.1                      | 36.3     <0.0001 |
| Uric acid (mg/dl) (mean (SD))                       | 5.8 (1.4)                | 5.7 (1.4)                 | 6.4 (1.5) <0.0001 |
| Glucose (mg/dl) (mean (SD))                         | 97.7 (8.8)               | 97.5 (8.8)                | 99.4 (8.8) <0.0001 |

**Women**

| No.                                                | 4,923                    | 4,454                     | 469      |
| Menopause status (%)                                |                          |                           | 0.6761   |
| Premenopausal                                       | 75.8                     | 75.8                      | 75.9     |
| Perimenopausal                                      | 6.3                      | 6.2                       | 7.2      |
| Postmenopausal                                      | 17.9                     | 18.0                      | 16.9     |

**Hormone replacement therapy use (%)¶**

| Ever (current or former)                            | 32.5                     | 33.0                      | 27.7     |
| Never                                              | 67.5                     | 67.1                      | 72.3     |

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* Based on χ² test for proportions (%) and t-tests for means.
† SD, standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein.
‡ Ratio of weight (kilograms) to standing height (meters) squared (kg/m²).
§ Baecke Index: 1 = low, 5 = high.
¶ Estrogen or estrogen plus progesterin.
in categorical covariates and incident hyperinsulinemia were, for the most part, consistent with associations at baseline—persons who had the most detrimental changes in covariates were most likely to develop hyperinsulinemia.

In continuous (table 4) and quintile (data not shown) analyses, increasing BMI, becoming obese, or sustaining obesity (obesity at both examinations) and starting to smoke were each associated with an increased risk of developing hyperinsulinemia according to both minimally and fully adjusted models. In minimally adjusted models, increasing triglycerides, increasing glucose values, and incident hypertension were positively associated with incident hyperinsulinemia.

### TABLE 2. Odds ratios* for baseline risk factors and hyperinsulinemia, Atherosclerosis Risk in Communities Study, 1987–1998

| Risk factor                                      | Minimal model† | Multivariable model‡ |
|-------------------------------------------------|----------------|---------------------|
| Age (years)                                     | 0.99           | 0.99                |
| Gender (men vs. women)                          | 1.00           | 0.65                |
| Education                                       |                |                     |
| <high school vs. >high school                   | 1.21           | 1.09                |
| High school vs. >high school                    | 1.00           | 0.97                |
| Race (Black vs. White)                          | 1.18           | 1.32                |
| Body mass index¶                                | 1.12           | 1.00                |
| Obese (≥30) vs. nonobese (<30)                  | 1.26           | 1.02                |
| Waist/hip ratio                                 | 1.41           | 1.35                |
| % of calories from carbohydrates                | 0.96           | 0.95                |
| Current cigarette smoking vs. never or former smoking | 1.30      | 1.29                |
| Current alcohol drinking vs. never drinking     | 0.96           | 0.95                |
| Sports-related physical activity#               | 0.94           | 0.98                |
| Total cholesterol                               | 0.94           | 0.94                |
| HDL§ cholesterol                                | 0.83           | 0.83                |
| LDL§ cholesterol                                | 1.00           | 0.96                |
| Triglycerides                                   | 0.94           | 0.87                |
| Factor VIII-C                                   | 0.96           | 0.98                |
| Factor VII                                      | 0.96           | 1.00                |
| Fibrinogen                                      | 1.03           | 1.00                |
| White blood cell count                          | 1.03           | 0.96                |
| Systolic blood pressure                         | 1.07           | 0.99                |
| Diastolic blood pressure                        | 1.02           | 0.94                |
| Hypertension (yes vs. no)                       | 1.01           | 1.03                |
| Uric acid                                       | 1.20           | 1.20                |
| Glucose                                         | 1.01           | 0.93                |

**Women (n = 4,932)**

| Menopause status                                |                |                     |
| Perimenopausal vs. premenopausal                 | 1.14           | 0.76                |
| Postmenopausal vs. premenopausal                 | 0.86           | 0.86                |
| Hormone replacement therapy use (ever vs. never) | 0.98           | 0.81                |

* Corrected for measurement error in baseline insulin concentration; odds ratios for continuous risk factors expressed for a level one standard deviation higher.
† Adjusted for age, gender, race, study center, and baseline insulin concentration.
‡ Three separate multivariable models were used to calculate odds ratios. A primary model that included body mass index was used to calculate all odds ratios. A second model was used to calculate odds ratios for obesity. A third model that included women only was used to calculate menopause status and hormone replacement therapy use. Total and LDL cholesterol as well as systolic and diastolic blood pressure were not included in multivariable models because of the potential for collinearity.
§ OR, odds ratio; CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein.
¶ Ratio of weight (kilograms) to standing height (meters) squared (kg/m²).
# Baecke Index: 1 = low, 5 = high.
Increasing concentrations of HDL cholesterol and, among women, using hormone replacement therapy were associated with a lower risk. However, in models that simultaneously adjusted for all risk factors, only changes in BMI, obesity, and smoking remained significantly predictive of hyperinsulinemia. Among women, ever use of hormone replacement therapy remained protective.

Secondary analyses

To evaluate the robustness of our results, we conducted a number of secondary analyses. First, we tested the association in the subpopulation with baseline insulin values below the 50th percentile by using cutpoints for hyperinsulinemia in both the full sample (90th percentile >19.1 μU/ml) and the 90th percentile in the lower half of the distribution (14.8 μU/ml). Next, in the full sample, we used the 75th percentile (13.7 μU/ml) to define hyperinsulinemia. In brief, all findings, with the exception of current smoking at baseline, which attenuated to nonsignificance, were similar regardless of the cutpoint used and were replicated in the subset with lower insulin values at baseline by using both cutpoints to define hyperinsulinemia.

We found evidence of some heterogeneity between risk factors for hyperinsulinemia by race and gender. However, because most of the observed heterogeneity by race and

**TABLE 3. Changes in risk factors during follow-up, Atherosclerosis Risk in Communities Study, 1987–1998**

| Change in risk factor | Total sample (n = 7,996) | Incident hyperinsulinemia |
|-----------------------|--------------------------|---------------------------|
|                       | Total sample (n = 8,139) | Yes (n = 903)             | p value* |
| Body mass index† (mean (SD‡)) | 1.49 (2.30) | 1.32 (2.25) | 2.74 (2.67) | <0.0001 |
| Obesity (body mass index ≥30) (%) | | | | |
| Became obese | 11.8 | 10.8 | 21.7 | <0.0001 |
| Became nonobese | 1.5 | 1.6 | 1.2 | |
| Obese at both examinations | 17.7 | 15.5 | 38.6 | |
| Nonobese at both examinations | 69.0 | 72.2 | 38.5 | |
| Waist/hip ratio (mean (SD)) | 0.031 (0.053) | 0.030 (0.054) | 0.027 (0.051) | 0.1246 |
| Cigarette smoking (%) | | | | <0.0001 |
| Started to smoke | 12.2 | 11.6 | 19.0 | |
| Stopped smoking | 2.0 | 2.2 | 0.6 | |
| Continued to smoke | 20.9 | 21.5 | 15.9 | |
| Never smoked | 64.8 | 64.8 | 64.5 | |
| Alcohol drinking (%) | | | | <0.0001 |
| Started to drink | 4.8 | 4.8 | 4.6 | |
| Stopped drinking | 13.5 | 13.4 | 14.7 | |
| Continued to drink | 48.6 | 49.4 | 40.5 | |
| Never drank | 33.1 | 32.4 | 40.3 | |
| Total cholesterol (mmol/liter) (mean (SD)) | –0.26 (0.88) | –0.30 (0.91) | –0.38 (1.01) | 0.0464 |
| HDL cholesterol (mmol/liter) (mean (SD)) | –0.07 (0.29) | –0.06 (0.29) | –0.10 (0.27) | 0.0003 |
| LDL cholesterol (mmol/liter) (mean (SD)) | –0.29 (0.83) | –0.33 (0.85) | –0.43 (0.91) | 0.0123 |
| Triglycerides (mmol/liter) (mean (SD)) | 0.23 (0.77) | 0.20 (0.75) | 0.36 (1.00) | <0.0001 |
| Incident hypertension (%) | 22.1 | 21.6 | 26.6 | 0.0016 |
| Glucose (mg/dl) (mean (SD)) | 4.12 (17.0) | 3.16 (16.1) | 15.0 (24.2) | <0.0001 |
| Women | | | | |
| No. | 4,724 | 4,291 | 433 | |
| Pre- or perimenopausal to postmenopausal (%) | 23.3 | 23.5 | 24.5 | 0.9316 |
| Hormone replacement therapy use (%)§ | | | | <0.0001 |
| Ever | 45.3 | 46.7 | 31.0 | |
| Never | 54.7 | 53.3 | 69.0 | |

* Based on χ² test for proportions (%) and t tests for means.
† Ratio of weight (kilograms) to standing height (meters) squared (kg/m²).
‡ SD, standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein.
§ Estrogen or estrogen plus progestin therapy.
gender was the result of a difference in the magnitude of the association rather than a difference in the direction of the association, and because we had no a priori hypothesis for this interaction, we do not describe it in detail in this paper.

**DISCUSSION**

While insulin resistance, and consequent hyperinsulinemia, has been suggested as the underlying cause of the metabolic syndrome, our data suggest a more complex relation. Consistent with previous research, we found that a central distribution of adiposity, concomitant weight gain, and development or maintenance of obesity predict progression to hyperinsulinemia—even after adjustment for baseline insulin concentrations. Our data further indicate that other metabolic syndrome components, namely, low HDL cholesterol levels and hyperuricemia, also precede the development of frank hyperinsulinemia. Additionally, our findings that cigarette smokers were at increased risk of developing hyperinsulinemia and that women who used hormone replacement therapy were at lower risk suggest a role for health behaviors.

**The metabolic syndrome: can hyperinsulinemia be detected first?**

Substantial evidence exists of a cross-sectional association between obesity and insulin resistance when hyperinsulinemia is used as the surrogate (7, 37, 38). Weight gain has been positively associated with increases in fasting serum insulin levels and insulin resistance (5, 6, 39, 40) in previous longitudinal studies. It has been proposed that weight gain is associated with a decline in the sensitivity of muscle tissue to the action of insulin, possibly by increasing

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**TABLE 4. Odds ratios* for changes in risk factors and incident hyperinsulinemia, Atherosclerosis Risk in Communities Study, 1987–1998**

| Change in risk factor                                      | Minimal model† | Multivariable model‡ |
|-----------------------------------------------------------|----------------|---------------------|
|                                                           | OR§ 95% CI§    | OR 95% CI           |
| Body mass index                                           | 1.94 1.80, 2.09| 1.74 1.57, 1.94     |
| Obesity                                                   |                |                     |
| Became obese vs. nonobese (at both examinations)          | 2.67 2.17, 3.29| 2.37 1.77, 3.16     |
| Became nonobese vs. nonobese                             | 0.57 0.29, 1.15| 0.75 0.30, 1.85     |
| Obese at both examinations vs. nonobese                  | 1.78 1.46, 2.18| 1.94 1.48, 2.54     |
| Waist/hip ratio                                           | 1.04 0.97, 1.12| 0.92 0.83, 1.02     |
| Current smoking                                           |                |                     |
| Started to smoke vs. never smoked                        | 2.16 1.66, 2.80| 1.66 1.23, 2.24     |
| Stopped smoking vs. never smoked                         | 0.38 0.15, 1.02| 0.34 0.10, 1.14     |
| Continued to smoke vs. never smoked                      | 0.88 0.68, 1.15| 0.91 0.68, 1.23     |
| Current alcohol drinking                                  |                |                     |
| Started to drink vs. never drank                         | 0.95 0.66, 1.36| 0.71 0.42, 1.22     |
| Stopped drinking vs. never drank                         | 1.05 0.83, 1.33| 0.96 0.69, 1.34     |
| Continued to drink vs. never drank                       | 0.93 0.77, 1.12| 1.03 0.79, 1.34     |
| Total cholesterol                                         | 1.06 0.98, 1.14| 0.89 0.80, 1.00     |
| HDL§ cholesterol                                          | 0.79 0.73, 0.86| 0.93 0.82, 1.04     |
| LDL§ cholesterol                                          | 0.98 0.91, 1.07|                     |
| Triglycerides                                             | 1.35 1.26, 1.45| 1.08 0.95, 1.22     |
| Glucose                                                   | 1.50 1.41, 1.59|                     |
| Incident hypertension (yes vs. no)                       | 1.28 1.07, 1.52| 1.19 0.93, 1.51     |
| Women (n = 4,724)                                         |                |                     |
| Pre- to postmenopausal                                    | 1.26 0.94, 1.67| 1.33 0.91, 1.93     |
| Hormone replacement therapy use (ever vs. never)          | 0.80 0.66, 0.97| 0.72 0.53, 0.98     |

* Corrected for measurement error in baseline insulin concentration; odds ratios for continuous risk factors expressed for a level one standard deviation higher.
† Adjusted for age, gender, race, study center, and baseline insulin concentration.
‡ Three separate multivariable models were used to calculate odds ratios. A primary model that included body mass index was used to calculate all odds ratios. A second model was used to calculate odds ratios for obesity. A third model that included women only was used to calculate menopause status and hormone replacement therapy use. LDL cholesterol and glucose were not included in multivariable models because of the potential for collinearity.
§ OR, odds ratio; CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein.
circulating free fatty acids, which can induce insulin resistance (41). Thus, more insulin is secreted to regulate glucose, resulting in hyperinsulinemia (7, 42). Obesity and weight gain are associated with an increase in several circulating inflammatory mediators, including tumor necrosis factor-alpha (43), which has been shown to interfere with the activity of the insulin receptor (44). Tumor necrosis factor-alpha, among other actions, increases IkappaB kinase beta (IKKbeta) activity, which blocks insulin signaling as well as releases nuclear factor kappa beta, which stimulates production of a number of inflammatory mediators (45). Additionally, obesity is associated with high levels of adipose tissue lipoprotein lipase. Several small studies have implicated adipose tissue lipoprotein lipase in the development of insulin resistance (46, 47).

It was unexpected that markers of inflammation such as white cell count and fibrinogen, which have been shown to predict incident diabetes (48), were not independent predictors of hyperinsulinemia. This finding suggests that, if inflammatory markers do reflect important independent causal pathways to diabetes, these pathways are mediated through, or at least better reflected by, concomitant baseline hyperinsulinemia.

Relatively fewer studies have examined uric acid as part of the metabolic syndrome (7, 10), but evidence suggests that hyperuricemia clusters very strongly with metabolic syndrome components. Little is known about why uric acid, thought to be an important antioxidant (49), is associated with metabolic syndrome risk. One hypothesis is that the kidneys are directly affected by increasing insulin levels and that urinary uric acid clearance decreases in proportion to increasing insulin resistance, thus increasing serum uric acid (50). Given our finding that hyperuricemia predicts incident hyperinsulinemia, this mechanism should be investigated further.

Health behaviors

In this sample, current cigarette smokers and persons who started smoking during the study were at increased risk of progressing to hyperinsulinemia. Cigarette smoking has been demonstrated to be a risk factor for incident diabetes mellitus in a number of longitudinal cohort studies, but the underlying mechanism remains unclear (14, 51, 52). In cross-sectional clinical research in populations of persons with (15) and without (13, 16) type 2 diabetes, cigarette smoking has been associated with higher levels of fasting insulin and decreased insulin sensitivity. Our data suggest that the increased risk of developing diabetes among cigarette smokers may be mediated by hyperinsulinemia or insulin resistance. However, our finding that only current smoking and starting to smoke, not continuing to smoke, are associated with elevated risks is contradictory. It may suggest either a spurious, although relatively strong, observation or the impact of shorter duration smoking, which attenuates with continued smoking, on other metabolic processes associated with hyperinsulinemia. More research is needed to investigate whether components of cigarette smoke, duration of smoking, or number of cigarettes smoked is associated with hyperinsulinemia.

The absence of an association between physical activity and hyperinsulinemia was unexpected, because the insulin-sensitizing effects of physical activity have been clearly demonstrated (12). Because effects of physical activity on insulin action are reversible, it is understandable that physical activity at baseline may not predict future changes. Alternatively, this finding could be attributed to difficulties in measuring physical activity. The Baecke Index (20), which we used to assess physical activity, has good validity and reliability (53) and has been associated with other cardiovascular risk factors. However, most ARIC Study participants were very inactive, so activity levels may be too homogeneous to capture differences.

One of the primary limitations of this study is the difficulty in implying causal effects based on observational epidemiology; debate surrounds the extent to which it can be done. Baseline insulin concentration was a strong predictor of hyperinsulinemia in this study, even when participants in the top baseline insulin decile were excluded or when the analysis was restricted to persons in the lower half of the insulin distribution at the baseline examination. However, it is still possible that persons with metabolic syndrome components at baseline who developed frank hyperinsulinemia during follow-up may have had atypically low insulin levels at baseline because of intrapatient variability and other sources of measurement error. They, more than others without metabolic syndrome components, may regress up to their usual (frequently hyperinsulinemic) values, which could account for the associations observed in this study. This possibility should be less likely because we attempted to reduce residual confounding by controlling for baseline insulin concentration in all analyses and replicating the analyses for persons with the lowest levels (<50th percentile) at baseline. However, given the lack of a standard definition of hyperinsulinemia, we were unable to eliminate “prevalent” cases from our analyses. Rather, a study design investigating the rate of change in insulin over follow-up would be more appropriate for evaluating the contribution of risk factors to elevations in fasting insulin levels.

BMI and waist/hip ratio are, at best, imprecise measures of adiposity. Correlations among BMI, waist/hip ratio, and adiposity measured by ultrasound are reasonably good (54), thus leading to their widespread use as estimates of adiposity and a central distribution of adiposity in epidemiologic studies and clinical practice. It is possible that our observed associations, and in particular the contradictory findings regarding baseline BMI and changes in BMI, are attributable to measurement error resulting from this estimate of adiposity. However, it is equally likely that the absence of an association with BMI in multivariable models at baseline reflects the larger contribution of waist/hip ratio in determining the risk of hyperinsulinemia (in minimally adjusted models, BMI is significant). This possibility is consistent with the hypothesis that metabolic risk is more closely associated with central versus peripheral adiposity. However, this explanation does not explain why an increase in waist/hip ratio over time does not confer the same risk in either minimally or multivariable adjusted models. We are surprised by this finding and speculate that, in this sample of participants who were already overweight at baseline and...
had a relatively high waist/hip ratio, there was little further variability in the rate of increase in waist/hip ratio.

Implications

Despite these limitations and some complex relations we observed, general patterns emerge from this novel study of an important metabolic pathologic condition. Our findings reemphasize the role of obesity and weight gain in progression to hyperinsulinemia and suggest important roles for lifestyle factors such as smoking and hormone replacement therapy. Evidence from this prospective investigation challenges established thinking that metabolic syndrome risk factors develop as a result of hyperinsulinemia.

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