# Fasting Hyperinsulinemia and Cardiovascular Disease Risk Factors in Nondiabetic Adults: Stronger Associations in Lean Versus Obese Subjects

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**The association between hyperinsulinemia and atherogenic risk factors has not been well studied in blacks and may be different for obese versus lean individuals. To investigate this possibility and to confirm the associations of hyperinsulinemia with cardiovascular disease risk factors in blacks and whites, we analyzed the joint associations of fasting serum insulin and obesity with risk factors in the Atherosclerosis Risk in Communities (ARIC) Study (1,293 black men, 4,797 white men, 2,033 black women, and 5,445 white women). Insulin values ≥90th percentile (≥21 μU/mL) constituted hyperinsulinemia; body mass index (BMI) values ≥27.3 kg/m² for women and ≥27.8 for men constituted obesity. Participants with hyperinsulinemia in all four race-sex groups had more atherogenic levels of most risk factors studied than those with normoinsulinemia. Among black men and women, mean levels of triglycerides, low-density lipoprotein cholesterol (LDL-C), apolipoprotein (apo) B, glucose, and fibrinogen (men only) were higher in hyperinsulinemic lean participants as compared with the normoinsulinemic obese group. Furthermore, most associations between insulin level and risk factors were stronger among lean versus obese subjects. For example, among lean black men, the difference in mean triglyceride concentration between those with hyperinsulinemia and those with normoinsulinemia was 147 − 99 = 48 mg/dL; among obese black men, the difference was 155 − 121 = 34 mg/dL ($P < .05$ for the interaction). Generally, similar negative interactions between BMI and insulin concentration were also observed among whites. We conclude that the association between hyperinsulinemia and many atherogenic risk factors holds for both blacks and whites and is stronger among lean versus obese adults.**


A POSITIVE ASSOCIATION between blood insulin level and coronary heart disease was first suggested in the 1960s[1,2] and has been confirmed in several prospective studies.[3-6] Insulin also has been associated positively with the occurrence of peripheral artery disease,[7] cerebrovascular disease,[8] and carotid artery wall thickness.[9,10]

The association between hyperinsulinemia and ischemic disease has several plausible explanations, including a direct effect of hyperinsulinemia on the arterial wall or an indirect effect on risk factors such as lipids, hemostatic factors, and/or blood pressure.[11] In vivo and in vitro studies have not demonstrated direct effects of insulin on the proliferation of arterial wall smooth muscle cells,[11] but hyperinsulinemia increases fatty acid synthetic activity and triglyceride content of arterial smooth muscle cells in animals.[12] Studies of normal and obese subjects have demonstrated that blood insulin is associated positively with total cholesterol and triglyceride levels[13-16] and associated inversely with high-density lipoprotein with cholesterol (HDL-C).[14,15] A weak positive association with low-density lipoprotein cholesterol (LDL-C) has also been demonstrated.[17,18] Other studies have reported positive associations of insulin with fibrinogen[19] and von Willebrand factor (vWF) activity.[20] A modest association has been reported between insulin level and blood pressure for normal subjects[13]; the association has been reported to be stronger among obese versus lean subjects[21] and among hypertensives versus normotensives.[22]

These associations have not been well studied in a large sample of nondiabetic black men and women. Furthermore, it is still uncertain whether insulin is related to physiological variables similarly in obese and lean subjects. Bonora et al[23] have reported higher blood pressure in hyperinsulinemics versus normoinsulinemics for lean subjects only. Lucas et al[21] have reported a stronger association between serum insulin and blood pressure for obese women versus lean women. Data from the Paris Prospective Study[24] have suggested that plasma insulin is more predictive of coronary heart disease mortality in obese men versus lean men. We therefore investigated the cross-sectional associations of serum insulin level with life-style factors, lipids, lipoproteins, hemostatic factors, and blood pressure in a study population of middle-aged blacks and whites. In addition, we examined the interaction between fasting serum insulin and obesity status. Our hypotheses were that coronary heart disease risk factors are less favorable for hyperinsulinemic individuals as compared with normoinsulinemics, and that these associations are similar for lean and obese participants.

## SUBJECTS AND METHODS

The Atherosclerosis Risk in Communities (ARIC) Study[25] is a prospective study of men and women aged 45 to 64 years at baseline. A total of 15,800 participants were selected from four communities: Forsyth County, NC; Jackson, MS; selected suburbs

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of Mineapolis, MN; and Washington County, MD. All Jackson participants and 14% of Forsyth County participants were black.

At baseline, in 1987 to 1989, participants completed a home interview that assessed their educational level, smoking habits, and personal and parental histories of diabetes and cardiovascular disease. After the home interview, participants were invited for a clinical examination that included assessment of other cardiovascular risk factors and a B-mode ultrasound examination of selected sites of the carotid arteries. The response rate (ie, the proportion of eligible subjects who completed the baseline examination) was 46% in Jackson and approximately 65% in each of the other three communities. A study of nonresponders to the ARIC examination suggested that they had less college education (22% *v* 35% in respondents), lower annual incomes, a higher incidence of long-term cigarette smoking (63% *v* 58%), and slightly poorer health.[25a] After a 12-hour fast, blood was drawn using a butterfly-vacutainer set from the antecubital vein of seated participants. Vacutainers containing serum separator gel (insulin and glucose) and EDTA plasma (lipids) were centrifuged at 3,000 × *g* at 4°C for 10 minutes. Aliquots were stored at −70°C. Samples were then shipped on dry ice to the central laboratories within 1 week of collection.

Fasting serum glucose level was measured by a hexokinase/glucose-6-phosphate dehydrogenase method. Fasting serum insulin level was measured by radioimmunoassay ($^{125}$Insulin Kit; Cambridge Medical Diagnostics, Billerica, MA). The reliability coefficient (between-subject variance divided by total variance obtained from repeated testing of a sample of individuals over several weeks) was .81. Total triglyceride[26] and cholesterol[27] levels were measured by enzymatic methods, with dextran-magnesium precipitation[28] for HDL-C. LDL-C level was calculated using the Friedewald equation.[29] Apolipoprotein (apo)A-I[30] and apo B[31] levels were measured by radioimmunoassays. Fibrinogen, factor VII, and factor VIII levels were measured by coagulation tests, vWF and protein C by enzyme-linked immunosorbent assays, and antithrombin III (AT III) by thrombin inactivation.[32] The standards for hemostasis assays were batches of universal coagulation reference plasma. Reliability coefficients (between-subject variance/total variance) obtained through repeated testing of a sample of subjects over 6 weeks were as follows: triglycerides, .85; LDL-C, .91; HDL-C, .94; apo A-I, .60; fibrinogen, .72; factor VII, .78; factor VIII, .86; vWF, .68; protein C, .56; and AT III, .42.

Measurements of weight (to the nearest pound [0.45 kg]) and height (to the nearest centimeter) were used to compute body mass index ([BMI] weight in kilograms divided by height in meters squared). Waist circumference at the umbilical level and maximum hip circumference were measured to the nearest centimeter, and waist to hip ratio (WHR) was calculated. Sitting blood pressure was measured three times after a 5-minute rest using a random-zero sphygmomanometer. Averages of the last two measurements of systolic and diastolic (5th-phase) pressure were used in the analyses. An index for physical activity in sports (sport index) ranging from 1 (low) to 5 (high) was derived.[33] Drinking status, the number of pregnancies, and the use of antihypertensive medications were assessed by interviews. Prevalent diabetes mellitus was defined as serum glucose ≥ 140 mg/dL (fasting) or ≥ 200 (nonfasting) and/or a history of diabetes or use of antidiabetic medications.

Of the 15,800 ARIC participants, 13,568 were included in the analyses (1,293 black men, 4,797 white men, 2,033 black women, and 5,445 white women). We excluded 1,561 participants with diabetes, 249 who were using lipid-lowering medications, and 422 who were missing laboratory values.

The aim of this cross-sectional analysis was to test the hypotheses that (1) compared with normoinsulinemia, fasting hyperinsulinemia is associated with more atherogenic profiles of lipids, hemostatic factors, and blood pressure, and (2) these associations are similar for lean and obese participants.

Univariate associations of fasting insulin with cardiovascular disease risk factors were examined by computing Pearson correlation coefficients. For ease of presentation of bivariate associations, participants were then categorized into four groups according to fasting insulin levels (hyperinsulinemia/normoinsulinemia) and obesity (obese/non-obese). Insulin values ≥ 90th percentile (≥ 21 μU/mL) were defined as hyperinsulinemia. Women with a BMI ≥ 27.3 kg/m$^2$ and men with a BMI ≥ 27.8 were defined as obese.[34] Unadjusted mean values of the risk factors were calculated for each insulin/obesity group. (Age adjustment was unnecessary because average ages were within 2 years among the four groups.) The interaction between insulin and obesity was tested for each cardiovascular disease risk factor using general linear modeling. These models used BMI and fasting serum insulin as continuous variables, as well as their cross-product interaction; because the main-effect variables (BMI and insulin) were associated at $P$ less than .05 with virtually all risk factors, only $P$ values for the interaction terms are presented. We also tested for quadratic relations between the cardiovascular risk factors of interest and fasting insulin and found no such relations. The SAS[35] computer package was used.

## RESULTS

The distributions of fasting serum insulin in nondiabetic men and women are shown in Fig 1. Serum insulin values were highest among black women and lowest among white women; insulin values were comparable among black and white men (Table 1).

Univariately, fasting serum insulin was correlated positively ($P < .001$) with BMI, WHR, gravidity, systolic blood pressure (whites only), triglycerides, LDL-C (blacks and white women only), apo B (blacks and white women only), glucose, fibrinogen (black women and whites only), factor VII, factor VIII, vWF, and protein C (Table 2). Serum insulin was negatively associated ($P < .001$) with the sport index (black women and whites only), HDL-C, and apo A-I. Cigarette smoking and AT III were not consistently associated with insulin. BMI and WHR were both associated with fasting serum insulin level, and those in the highest quartiles of both had the highest insulin levels (Fig 2). Adjustment for age and BMI attenuated the univariate correlations shown (Table 2), reflecting the shared contribution of BMI and insulin, but the patterns of association for insulin largely remained.

Sex-specific characteristics of participants are listed according to insulin and obesity strata in Table 3. (Although stratification facilitates data depiction, there was some residual confounding. That is, within each insulin group, mean insulin level was somewhat higher in the obese group than in the lean, and within each obesity group, mean BMI was slightly higher in hyperinsulinemics *v* normoinsulinemics. Thus, statistical tests for associations with insulin and BMI and their interaction were based on continuous variables.) Mean WHR was lowest in the normoinsulinemic lean group and highest in the hyperinsulinemic obese group. The difference in mean WHR between hyperinsulinemics and normoinsulinemics was larger for lean participants (0.037 in black men, 0.031 in white men, 0.049 in black women, and 0.069 in white women) than for the obese

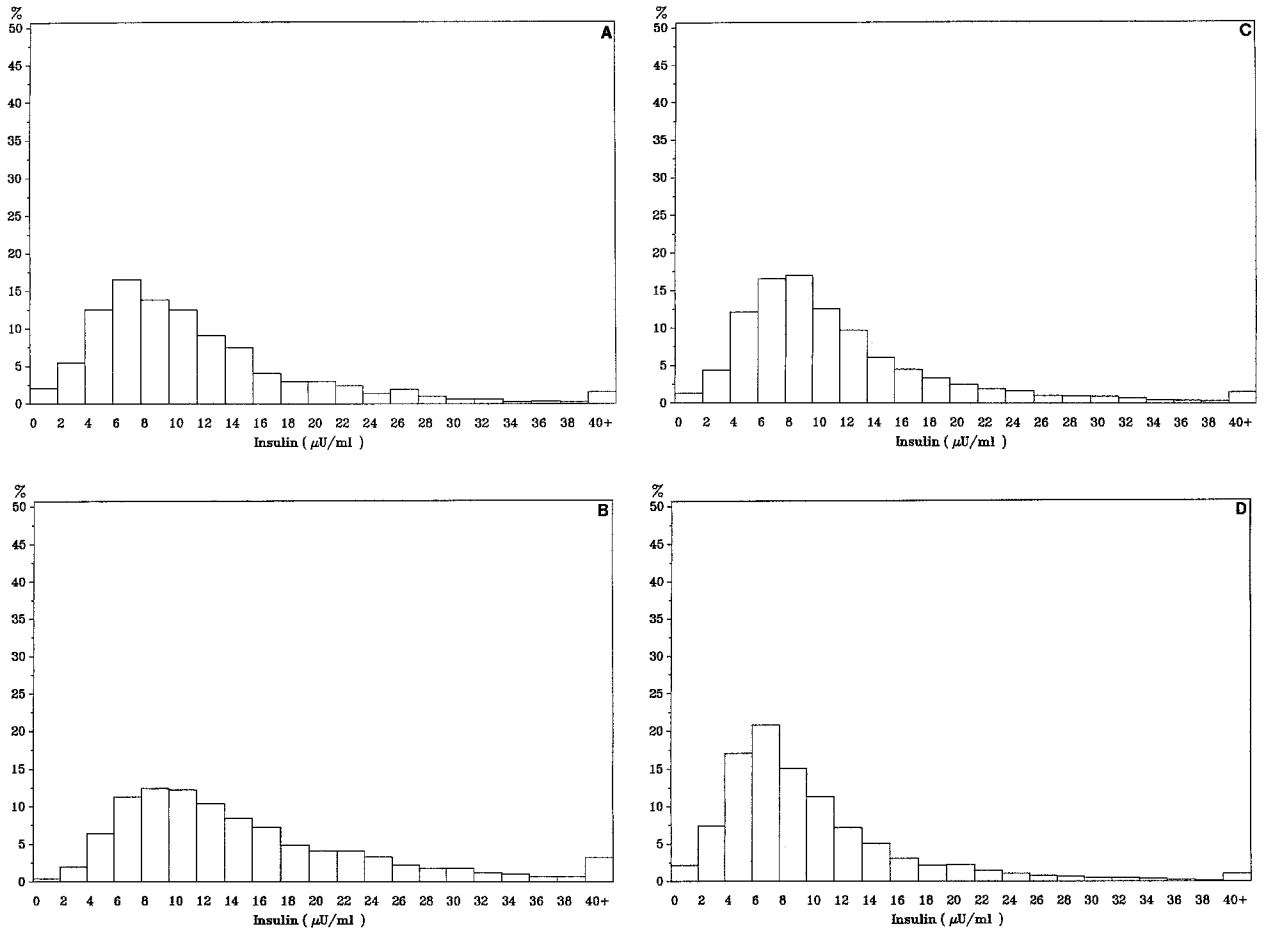


**Fig 1. Distribution of fasting serum insulin among nondiabetic adults. (A) Black men; (B) black women; (C) white men; (D) white women (ARIC, 1987-1989).**

(0.024 in black men, 0.024 in white men, 0.039 in black women, and 0.043 in white women) ($P < .05$ for the interaction). For blacks, lean men had a lower mean sports index than obese men; hyperinsulinemic lean black men had the lowest sports index. However, for whites, lean men had a higher mean sports index than obese men; hyperinsulinemic obese white men had the lowest sports index. Both black and white hyperinsulinemic women had a lower mean sports index than normoinsulinemics; hyperinsulinemic obese women had the lowest index. Other characteristics of the insulin/obesity groups are listed in Table 3. Generally, findings for whites were similar to blacks.

Sex-specific mean values of plasma lipids, lipoproteins, and blood pressure for each insulin/obesity group are listed in Table 4. As compared with normoinsulinemics, hyperinsulinemics had more atherogenic profiles of plasma lipids, lipoproteins, and serum glucose. Furthermore, for most of these risk factors, the difference in mean values between those with hyperinsulinemia and those with normoinsulinemia was larger for lean than for obese participants. For both blacks and whites, this interaction between BMI and insulin level (analyzed as continuous variables) was statistically significant ($P < .05$) in both sexes for all plasma lipids and lipoproteins and for serum glucose. In whites but not in blacks, hyperinsulinemia was associated with increased blood pressure. In blacks, and in contrast with lipids, systolic and diastolic blood pressure measurements were comparable among the four groups. Among both blacks and whites, normoinsulinemic obese participants generally had less atherogenic profiles than hyperinsulinemic lean ones. Differences in mean plasma lipids, lipoproteins, and serum glucose associated with obesity level were less for normoinsulinemics than for hyperinsulinemics, except for triglycerides, HDL-C, and apo A-I for black women and LDL-C and apo B for black men and white women.

**Table 1. Race- and Sex-Specific Distribution of Fasting Serum Insulin (μU/mL) in the ARIC Study, 1987-1989**

| Race/Sex Group* | Mean | Median | Percentile 25th | Percentile 75th |
|---|---|---|---|---|
| Black men (n = 1,293) | 11.4 | 9 | 6 | 14 |
| White men (n = 4,797) | 11.2 | 9 | 6 | 13 |
| Black women (n = 2,033) | 14.8 | 12 | 8 | 18 |
| White women (n = 5,445) | 9.5 | 8 | 5 | 11 |

*Only nondiabetics were included.

Table 5 lists mean values of hemostatic factors for the four insulin/obesity groups for both blacks and whites. In blacks, mean fibrinogen levels were higher in hyperinsulinemics versus normoinsulinemics, with the highest mean values in hyperinsulinemic obese groups. Mean values for

**Table 2. Correlations Between Fasting Serum Insulin and Risk Factors in the ARIC Study, 1987-1989**

| Variable | Whites | | | | Blacks | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate | | Partial‡ | | Univariate | | Partial‡ | |
| | Men (n = 4,797)† | Women (n = 5,445)† | Men (n = 4,621)† | Women (n = 5,399)† | Men (n = 1,293)† | Women (n = 2,033)† | Men (n = 1,235)† | Women (n = 1,956)† |
| BMI (kg/m²) | .48 | .50 | — | — | .55 | .40 | — | — |
| WHR | .37 | .40 | .14 | .19 | .40 | .35 | .13 | .20 |
| Cigarette-years of smoking§ | .08 | .01* | .07 | .05 | −.06* | −.01* | .00* | .02* |
| Sports index | −.12 | −.11 | −.07 | −.05 | .04* | −.09 | −.00* | −.07 |
| Gravidity | — | .05 | — | −.02* | — | .12 | — | .06* |
| Systolic BP (mm Hg) | .18 | .24 | .10 | .11 | −.00* | .03* | −.08* | −.03* |
| Triglycerides (mg/dL) | .32 | .37 | .25 | .28 | .28 | .27 | .30 | .29 |
| LDL-C (mg/dL) | −.03* | .11 | −.06 | .04 | .14 | .11 | .07* | .11 |
| HDL-C (mg/dL) | −.28 | −.35 | −.18 | −.22 | −.31 | −.28 | −.18 | −.23 |
| Apo A-I (mg/dL) | −.15 | −.23 | −.09 | −.14 | −.19 | −.17 | −.09 | −.13 |
| Apo B (mg/dL) | .06 | .17 | .02* | .10 | .16 | .15 | .10 | .15 |
| Glucose (mg/dL) | .32 | .42 | .24 | .31 | .35 | .40 | .29 | .36 |
| Fibrinogen (mg/dL) | .08 | .19 | .04* | .08 | .08* | .13 | .05* | .03* |
| Factor VII (%) | .19 | .21 | .14 | .11 | .14 | .14 | .10 | .11 |
| Factor VIII (%) | .15 | .21 | .12 | .13 | .17 | .16 | .17 | .14 |
| vWF (%) | .13 | .18 | .11 | .11 | .11 | .13 | .15 | .09 |
| AT III (%) | −.05* | .04* | −.03* | .05 | .01* | .01* | .03* | .04* |
| Protein C (μg/mL) | .05 | .12 | .03* | .07 | .11 | .14 | .06* | .13 |

NOTE. All correlations were statistically significant at $P < .001$ except where noted by an asterisk.

Abbreviation: BP, blood pressure.

†Maximum n for each group.

‡Adjusted for age and BMI (kg/m²).

§Average number of cigars/cigarettes per day times number of years smoked.

protein C were higher in obese versus lean subjects and, among women, were also higher in hyperinsulinemics than in normoinsulinemics. For fibrinogen (in men only) and protein C (in both sexes), the interaction between BMI and insulin level was statistically significant ($P < .05$), but in this case the difference in values between hyperinsulinemics and normoinsulinemics was larger for obese than for lean subjects. Among men, mean values of factor VII, factor VIII, and vWF were highest in the hyperinsulinemic obese group than in the other three groups; mean AT III

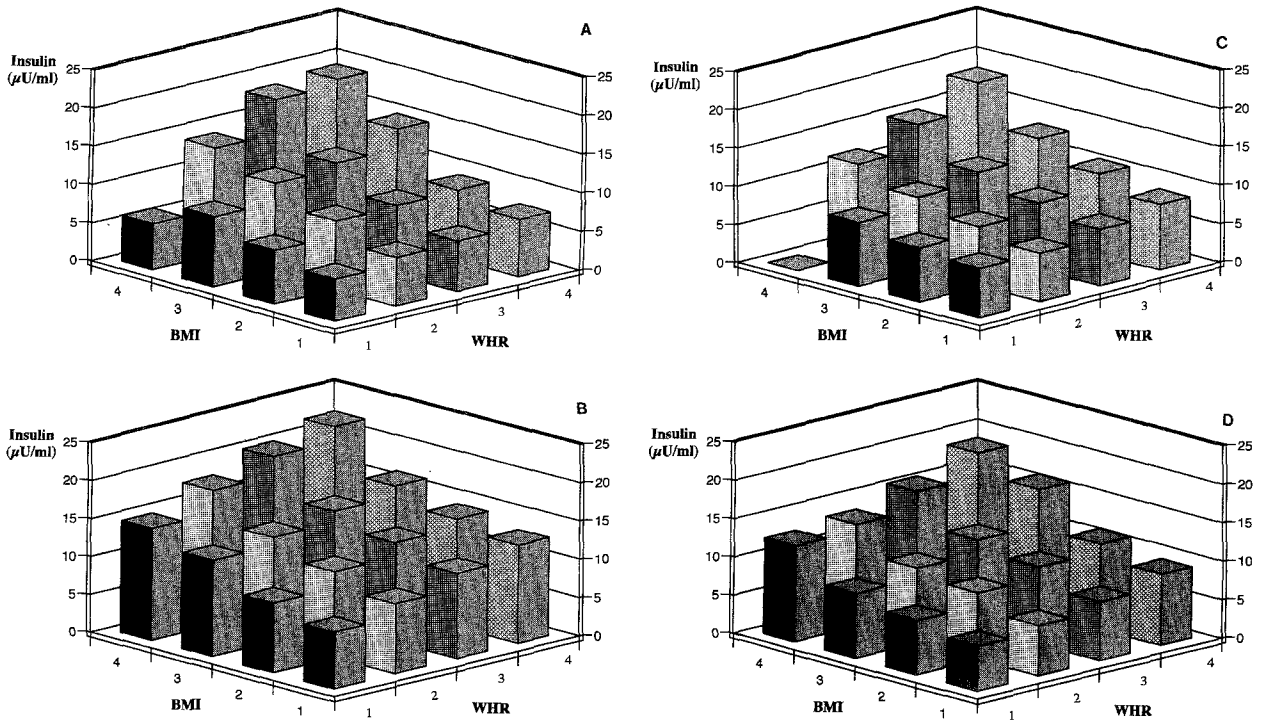


**Fig 2. Mean values of fasting serum insulin by quartiles of BMI (kg/m²) and WHR. (A) Black men; (B) black women; (C) white men; (D) white women (ARIC, 1987-1989).**

**Table 3. Sex- and Race-Specific Values of Life-style Factors and Family History by Level of Obesity and Fasting Serum Insulin Status in the ARIC Study, 1987-1989**

| | Whites | | | | Blacks | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| Variable | Lean | Obese | Lean | Obese | Lean | Obese | Lean | Obese |
| No. of subjects* | | | | | | | | |
| Normoinsulinemic | 2,841 | 1,476 | 3,518 | 1,574 | 727 | 414 | 694 | 911 |
| Hyperinsulinemic | 82 | 400 | 56 | 297 | 21 | 131 | 39 | 389 |
| Mean age, years | | | | | | | | |
| Normoinsulinemic | 55 | 55 | 54 | 54 | 54 | 54 | 53 | 53 |
| Hyperinsulinemic | 57 | 54 | 56 | 54 | 55 | 53 | 54 | 53 |
| Insulin (μU/mL) | | | | | | | | |
| Normoinsulinemic | 8 | 11 | 7 | 11 | 8 | 12 | 9 | 12 |
| Hyperinsulinemic | 29 | 30 | 28 | 30 | 25 | 30 | 26 | 31 |
| BMI (kg/m$^2$) | | | | | | | | |
| Normoinsulinemic | 25 | 31 | 23 | 32 | 24 | 31 | 24 | 33 |
| Hyperinsulinemic | 26 | 33 | 25 | 35 | 26 | 33 | 25 | 35 |
| Mean WHR | | | | | | | | |
| Normoinsulinemic | 0.947 † | 0.991 | 0.861 † | 0.924 | 0.911 † | 0.961 | 0.852 † | 0.908 |
| Hyperinsulinemic | 0.978 | 1.015 | 0.930 | 0.967 | 0.948 | 0.985 | 0.901 | 0.947 |
| Mean sports index | | | | | | | | |
| Normoinsulinemic | 2.74 | 2.64 | 2.49 † | 2.32 | 2.24 | 2.30 | 2.16 | 2.10 |
| Hyperinsulinemic | 2.53 | 2.46 | 2.52 | 2.19 | 2.05 | 2.32 | 2.06 | 2.01 |
| Gravidity (n) | | | | | | | | |
| Normoinsulinemic | — | — | 3 | 3 | — | — | 4 | 5 |
| Hyperinsulinemic | — | — | 3 | 3 | — | — | 5 | 5 |
| Current drinkers (%) | | | | | | | | |
| Normoinsulinemic | 70 | 72 | 66 | 57 | 55 | 49 | 32 | 20 |
| Hyperinsulinemic | 70 | 67 | 55 | 46 | 50 | 42 | 23 | 16 |
| Current smokers (%) | | | | | | | | |
| Normoinsulinemic | 28 | 20 | 29 | 18 | 46 | 26 | 34 | 22 |
| Hyperinsulinemic | 22 | 19 | 20 | 18 | 33 | 33 | 29 | 19 |
| Parental history of diabetes (% yes) | | | | | | | | |
| Normoinsulinemic | 19 | 24 | 20 | 27 | 26 | 25 | 24 | 32 |
| Hyperinsulinemic | 17 | 25 | 20 | 24 | 29 | 31 | 29 | 34 |
| Parental history of CVD (% yes) | | | | | | | | |
| Normoinsulinemic | 63 | 64 | 65 | 67 | 49 | 50 | 55 | 61 |
| Hyperinsulinemic | 71 | 60 | 84 | 64 | 69 | 59 | 76 | 65 |

Abbreviation: CVD, cardiovascular disease.

*Maximum n for each group.

†Significant BMI × insulin interaction term at $P < .05$.

was lowest in the hyperinsulinemic lean group. Among women, factor VII was highest in the hyperinsulinemic obese group, factor VIII and vWF were highest in the hyperinsulinemic lean group, and AT III was higher among lean versus obese subjects. Interaction terms between BMI and insulin level were not significant for factor VII, factor VIII, vWF, or AT III in either sex. Hemostatic variables were associated with the insulin/obesity groups differently in whites as compared with blacks (Table 5). In whites, the interaction between BMI and insulin level was statistically significant ($P < .05$) for fibrinogen and AT III (in women only) and for factor VII and protein C (in both sexes). Also, in contrast to blacks, in whites the difference in values between hyperinsulinemics and normoinsulinemics was typically larger for the lean than for the obese. In both white men and women, factor VIII and vWF were highest in the hyperinsulinemic lean group and the interaction terms between BMI and insulin level were not statistically significant for factor VIII or vWF.

## DISCUSSION

Prospective studies have shown that an elevated fasting insulin level is associated with increased risk of coronary heart disease.[3-5] Experimental studies have shown that insulin may have direct biologic effects on the arterial wall.[36] However, an indirect effect of insulin on the arterial wall is clearly likely, because hyperinsulinemia is linked to atherogenic cardiovascular risk factors including obesity, hyperlipidemia, and high blood pressure.[37,38] These associations with cardiovascular risk factors have been studied predominantly in whites. We sought to confirm such associations in nondiabetic middle-aged blacks as well. This is especially pertinent because of the higher rate of diabetes in black versus white Americans.[39] We were also interested in whether such associations differed for obese versus lean participants. Few previous studies have suggested an interaction between obesity and hyperinsulinemia for blood pressure,[21,23,40] and Fontbonne et al[24] have reported an

**Table 4. Sex- and Race-Specific Values of Plasma Lipids and Blood Pressure by Level of Obesity and Fasting Serum Insulin Status in the ARIC Study, 1987-1989**

| | Whites | | | | Blacks | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| Variable | Lean | Obese | Lean | Obese | Lean | Obese | Lean | Obese |
| Triglycerides (mg/dL) | | | | | | | | |
| Normoinsulinemic | 126 * | 153 | 108 * | 136 | 99 * | 121 | 93 * | 95 |
| Hyperinsulinemic | 198 | 202 | 182 | 193 | 147 | 155 | 145 | 128 |
| LDL-C (mg/dL) | | | | | | | | |
| Normoinsulinemic | 138 | 140 | 130 * | 139 | 130 * | 143 | 130 * | 134 |
| Hyperinsulinemic | 131 | 132 | 140 | 138 | 154 | 144 | 137 | 145 |
| Apo B (mg/dL) | | | | | | | | |
| Normoinsulinemic | 94 * | 98 | 88 * | 94 | 88 * | 96 | 86 * | 88 |
| Hyperinsulinemic | 91 | 97 | 105 | 101 | 105 | 100 | 94 | 97 |
| HDL-C (mg/dL) | | | | | | | | |
| Normoinsulinemic | 47 * | 42 | 64 * | 55 | 57 * | 49 | 67 * | 61 |
| Hyperinsulinemic | 39 | 37 | 49 | 45 | 49 | 42 | 50 | 53 |
| Apo A-I (mg/dL) | | | | | | | | |
| Normoinsulinemic | 122 * | 117 | 148 * | 136 | 137 * | 128 | 152 * | 145 |
| Hyperinsulinemic | 116 | 111 | 127 | 124 | 132 | 120 | 132 | 137 |
| Glucose (mg/dL) | | | | | | | | |
| Normoinsulinemic | 100 | 103 | 95 * | 99 | 98 * | 101 | 96 * | 98 |
| Hyperinsulinemic | 106 | 109 | 107 | 108 | 103 | 109 | 102 | 107 |
| Systolic BP (mm Hg)† | | | | | | | | |
| Normoinsulinemic | 118 | 121 | 114 * | 120 | 129 | 130 | 125 | 128 |
| Hyperinsulinemic | 123 | 124 | 118 | 125 | 128 | 128 | 120 | 127 |
| Diastolic BP (mm Hg)† | | | | | | | | |
| Normoinsulinemic | 72 | 75 | 69 * | 72 | 82 | 84 | 77 | 79 |
| Hyperinsulinemic | 75 | 77 | 70 | 74 | 82 | 82 | 76 | 79 |

*Significant BMI × insulin interaction term at $P < .05$.
†Adjusted for antihypertensive medication use.

interaction between fasting plasma insulin and obesity for coronary heart disease death.

Several issues warrant consideration for proper interpretation of our findings. First, in nondiabetic subjects, fasting serum insulin level is not a perfect measure of insulin resistance or insulin secretion.[41,42] However, there is a reasonably good correlation between fasting insulin and clamp measures of insulin resistance.[42,43] Second, cardiovas-

**Table 5. Sex- and Race-Specific Values of Hemostatic Factors by Level of Obesity and Fasting Serum Insulin Status in the ARIC Study, 1987-1989**

| | Whites | | | | Blacks | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| Variable | Lean | Obese | Lean | Obese | Lean | Obese | Lean | Obese |
| Fibrinogen (mg/dL) | | | | | | | | |
| Normoinsulinemic | 290 | 295 | 289 * | 311 | 303 * | 300 | 308 | 328 |
| Hyperinsulinemic | 307 | 307 | 308 | 326 | 318 | 321 | 313 | 339 |
| Factor VII (%) | | | | | | | | |
| Normoinsulinemic | 109 * | 113 | 120 * | 130 | 108 | 110 | 117 | 121 |
| Hyperinsulinemic | 120 | 121 | 136 | 140 | 110 | 118 | 119 | 129 |
| Factor VIII (%) | | | | | | | | |
| Normoinsulinemic | 120 | 121 | 122 | 129 | 138 | 136 | 139 | 143 |
| Hyperinsulinemic | 135 | 132 | 144 | 143 | 137 | 153 | 158 | 154 |
| vWF (%) | | | | | | | | |
| Normoinsulinemic | 111 | 111 | 106 | 113 | 129 | 123 | 123 | 131 |
| Hyperinsulinemic | 136 | 123 | 132 | 130 | 139 | 142 | 151 | 142 |
| AT III (%) | | | | | | | | |
| Normoinsulinemic | 109 | 106 | 111 * | 112 | 113 | 111 | 117 | 114 |
| Hyperinsulinemic | 107 | 106 | 115 | 112 | 104 | 113 | 117 | 114 |
| Protein C (μg/mL) | | | | | | | | |
| Normoinsulinemic | 3.02 * | 3.08 | 3.21 * | 3.33 | 2.94 * | 3.04 | 3.11 * | 3.14 |
| Hyperinsulinemic | 3.14 | 3.06 | 3.36 | 3.45 | 2.93 | 3.05 | 3.16 | 3.35 |

*Significant BMI × insulin interaction term at $P < .05$.

cular risk factors have considerable intercorrelations, which makes it difficult to determine which associations are true effects of hyperinsulinemia. Finally, the response rate for black participants in the ARIC was 46%, which makes response bias a potential concern. However, associations observed for blacks were similar to those for whites (response rate, 65%). Furthermore, it seems unlikely that physiologic associations between insulin and other factors would be different in responders and nonresponders.

The variables associated with insulin in Table 3 are more likely determinants of insulin level than a consequence of it. It is well established that BMI[44] and WHR[44] are determinants of insulin level, and Fig 2 indicated clearly that both contributed. Insulin was also associated inversely with the sports index, as reported previously.[44]

Many previous reports have shown that fasting serum insulin is associated positively with blood triglycerides,[16,17,38,45] LDL-C,[17] and apo B[45] and negatively with HDL-C[16,17,38,45] and apo A.[45] Our results corroborate that hyperinsulinemia is similarly associated with these lipids in both blacks and whites. The Coronary Artery Risk Development in Young Adults Study (CARDIA)[15] reported similar correlations between fasting serum insulin and blood lipids for both black and white participants aged 18 to 30 years. In both studies, fasting serum insulin was highest among black women, and insulin showed the strongest association with BMI ($r$ = .50 in CARDIA, $r$ = .40 to .55 in ARIC). In both studies, triglyceride was the lipid variable most strongly associated with insulin, and the association was stronger in whites than in blacks. Insulin resistance (and hyperinsulinemia) is associated with increased adipose tissue lipolysis and circulating free fatty acids and overproduction of very-low-density lipoprotein triglycerides.[46,47] It also increases chylomicron and very-low-density lipoprotein catabolism in the circulation,[48] which may explain its negative association with HDL-C.

Previous reports have consistently connected hyperinsulinemia with impaired fibrinolysis.[49,50] Diabetes and impaired glucose tolerance are associated with higher levels of fibrinogen, factors VII, VIII, and X, and vWF.[20,51] We found that fasting serum insulin positively correlated with several hemostatic variables: fibrinogen, factor VII, factor VIII, vWF, and protein C. The interaction of hyperinsulinemia and obesity with hemostatic factors appeared to differ between blacks and whites (Table 2). This finding could have arisen by chance and thus warrants corroboration. However, there is some clinical evidence of differences between blacks and whites in response to thrombolytic agents.[52]

Fasting serum insulin had almost no correlation with systolic blood pressure in black participants. Correlations were stronger, statistically significant, and positive in whites. In contrast, nondiabetic blacks and whites had similar blood pressure–insulin associations in the CARDIA Study[15] and in the study reported by Saad et al.[53] Insulin may affect blood pressure by two mechanisms: first, via insulin-induced renal reabsorption of sodium, which can induce a positive sodium balance and favor extravascular shift of fluids and sodium[54]; and second, via the sympathetic nervous system, it may influence circulating norepinephrine, thereby increasing peripheral vascular resistance.[53,55] On the other hand, insulin infusion[56] and the hyperinsulinemia of insulinoma[57] do not seem to elevate blood pressure. Other studies (predominantly in whites) have shown either strong,[21] weak,[13,15] or no[58] association between plasma insulin concentration and blood pressure in both lean[58] and obese[21] individuals. Christlieb et al[40] found an association between insulin and blood pressure in obese but not in lean subjects. Bonora et al[23] reported higher systolic and diastolic blood pressure in lean but not in obese hyperinsulinemics as compared with sex-, age-, and weight-matched normoinsulinemics. It therefore remains to be determined whether hyperinsulinemia is a true cause of elevated blood pressure.

For many risk factors and in both blacks and whites, we found a negative statistical interaction between insulin and BMI, indicating that the association of insulin with risk factors is stronger for leaner individuals. It is unclear why, but perhaps lean hyperinsulinemic individuals have hyperinsulinemia that is more genetically determined through mechanisms of an inherited nature; and it could be accompanied, for example, by more sympathetic nervous system dysfunction. Insulin resistance and hyperinsulinemia occur in obesity apparently because of increased lipid oxidation and decreased glucose utilization,[59] whereas in lean subjects hyperinsulinemia may have a different etiology and a different set of consequences. Regardless, being obese and normoinsulinemic appears to carry a less hazardous physiologic profile than being lean and hyperinsulinemic. Heterogeneity of insulin levels among the obese may explain why BMI often shows a U-shape or no association with mortality.[10]

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