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Insulin resistance predicts future deterioration of glucose tolerance in nondiabetic young African Americans

Yonghong Huan[a,*], Harvey Kushner[b], Bonita Falkner[a]

[a]Division of Nephrology, Department of Medicine, Thomas Jefferson University, Philadelphia, PA 19107, USA
[b]BioMedical Computer Research Institute, Inc, Philadelphia, PA, USA

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Abstract

Insulin resistance has been linked to the development of type 2 diabetes mellitus and increased cardiovascular risk in several high-risk populations. The purpose of this study was to determine if insulin resistance measured by insulin clamp can predict deterioration of glucose metabolism and increased cardiovascular risk in nondiabetic young adult African Americans. Nondiabetic young African American men (n = 60) and women (n = 114) were enrolled. Measurements obtained included blood pressure, anthropometrics, plasma lipids, oral glucose tolerance test, and insulin sensitivity by insulin clamp. Participants were reexamined 8 years later. The relationship between insulin sensitivity and glucose metabolism was analyzed using a 2-way analysis of variance with body mass index at the initial examination as a covariate. After adjusting for the significant difference of body mass index between the insulin-resistant and insulin-sensitive groups, insulin resistance predicted statistically significant worsening glucose metabolism, developing diabetes, and increasing risk factors for cardiovascular disease.

1. Introduction

Type 2 diabetes mellitus is the most common form of diabetes and has been increasing at an alarming rate. African Americans are affected by type 2 diabetes mellitus at a disproportionately greater rate than white Americans [1]. Both diabetes and prediabetes are commonly associated with multiple risk factors designated as the *metabolic syndrome*. The presence of metabolic syndrome with or without clinical diabetes increases markedly the risk for cardiovascular morbidity and mortality [2,3]. Insulin resistance contributes to the pathogenesis of type 2 diabetes mellitus [4] and is linked with increased cardiovascular risks even in the prediabetic state [5]. Most of the data that establish the relationship of insulin resistance with diabetes risk are derived from cross-sectional studies. Little information is available on African Americans that documents progression from insulin resistance to diabetes. The euglycemic insulin clamp procedure is regarded as the criterion standard for measurement of insulin sensitivity [6]. The purpose of this study was to determine if insulin resistance measured by insulin clamp predicts the deterioration of glucose metabolism and increased cardiovascular risk status in nondiabetic young adult African Americans.

2. Methods

2.1. Clinical sample

A longitudinal analysis was conducted on data obtained from a cohort of healthy young adult African Americans. An initial examination (examination 1) was performed on young adults at ages 20 to 42 years. Subjects who agreed to participate in the follow-up study were reexamined approximately 8 years later at ages 28 to 52 years (examination 2). Written informed consent was obtained from each participant at the time of initial enrollment and again at reenrollment on an institutionally approved protocol and consent form. Exclusion criteria at examination 1 included known type 1 diabetes mellitus and type 2 diabetes mellitus, polycystic ovarian syndrome, and chronic kidney disease (serum creatinine >2.0 mg/dL). The clinical assessments at examinations 1 and 2 included anthropometric data, blood pressure (BP), plasma lipid levels, oral

* Corresponding author. Tel.: +1 215 503 2501; fax: +1 215 503 2506.
E-mail address: yonghong.huan@jefferson.edu (Y. Huan).

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glucose tolerance test (OGTT), and insulin sensitivity measured by the insulin clamp.

2.2. Procedures

Anthropometric measurements included height, weight, and skinfold thickness of 4 sites: the triceps, biceps, subscapular, and suprailiac [7]. Body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (in square meters). Anthropometric measurements were used to estimate the percentage of body fat and fat-free mass [7,8]. Blood pressure measurements were obtained from each subject after a 10-minute rest period in a seated position using auscultation with a mercury column sphygmomanometer. The average of 2 successive readings of systolic and diastolic (Korotkoff phase V) was used as the BP. The OGTT was conducted after a 12-hour overnight fast. A fasting blood sample was obtained for plasma lipids, insulin, and glucose before the ingestion of 75 g of glucose solution (Glucola; Ames Diagnostics, Elkhart, IN). Blood samples were obtained at 30, 60, and 120 minutes postingestion and were assayed for plasma insulin and glucose concentrations. The value of sum insulin was computed by summing up the plasma insulin levels at fasting and at 30, 60, and 120 minutes.

Insulin sensitivity was assessed using insulin-stimulated glucose uptake measured by the euglycemic hyperinsulinemic clamp technique as previously described [6,9,10]. In brief, all subjects were required to have a 12-hour overnight fast before the insulin clamp procedure. Blood samples were obtained for baseline plasma glucose and insulin concentration. Hyperinsulinemia was established with a primed constant infusion of insulin (Eli Lilly, Indianapolis, IN) at a concentration of 1000 mU/mL in isotonic sodium chloride solution according to the method of Rizza et al [9]. The primed infusion rate was sufficient to achieve steady-state hyperinsulinemia at 80 to 120 μU/mL above fasting insulin levels with the goal of suppressing hepatic glucose production. Hyperinsulinemia was maintained for 120 minutes, during which time euglycemia was achieved using a variable infusion of 20% dextrose in water (Abbott Laboratories, Abbott Park, IL). The glucose infusion rate was adjusted by the negative feedback equation of DeFronzo et al [6] according to plasma glucose sampled every 10 minutes.

The insulin-stimulated glucose uptake (M) was computed as the mean glucose infusion during the final 60 minutes of the procedure and expressed as milligrams per kilogram per minute. Higher values of M were indicative of greater insulin sensitivity. Because the level of steady-state hyperinsulinemia achieved during the clamp procedure varied slightly among the participants, an index of insulin sensitivity (M/I) was calculated by dividing the glucose infusion rate (M) by the mean insulin level (I) achieved during the final 60 minutes of steady-state hyperinsulinemia. Because adipose tissue is more insulin resistant relative to muscle tissue, the measured insulin-mediated glucose uptake was adjusted for adiposity. Using the estimated fat-free mass, the insulin-stimulated glucose uptake was calculated in milligrams per kilogram of fat-free mass per minute (M'). The adjusted index of insulin sensitivity was also corrected for hyperinsulinemia and expressed as M'/I.

A fasting blood sample was sent to the Lipid Disease Laboratory at the Medical College of Pennsylvania at examination 1 and to the Lipid Laboratory at Thomas Jefferson University at examination 2. At both laboratories, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were analyzed with standard enzymatic methods and an automated analyzer (Hitachi 704). The HDL-C was isolated according to the method of Bachorik et al [11]. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation [12]. Plasma glucose concentration was analyzed with the glucose oxidase technique (YS Model 27; Glucostat, Yellow Springs, OH). Plasma insulin concentration was determined with a solid phase radioimmunoassay (Coat-a-Count; Diagnostic Products, Los Angeles, CA). Coefficients of variation for inter- and intraassay variability for glucose, insulin, and lipid assays were less than 5%.

Glucose tolerance status was determined according to the American Diabetic Association (ADA) criteria [13]. *Normal glucose tolerance* (*NGT*) was defined as fasting glucose less than 100 mg/dL and 2-hour OGTT glucose less than 140 mg/dL. *Abnormal* (or *prediabetic*) *glucose tolerance* was defined as fasting glucose of 100 to 125 mg/dL and/or 2-hour OGTT glucose in the range of 140 to 199 mg/dL. Because of variability in fasting plasma glucose, 2 separate plasma glucose values between 100 and 125 mg/dL were required for designation of impaired fasting glucose. *Diabetes* was defined according to the ADA definition as fasting glucose of at least 126 mg/dL and/or 2-hour OGTT glucose of at least 200 mg/dL. *Metabolic syndrome* was defined according to the Adult Treatment Panel (ATP) III definition [14] as having at least 3 of the following criteria: high BP ($\geq$130/85 mm Hg), high triglyceride level ($\geq$150 mg/dL), low HDL-C level (<40 mg/dL for men or <45 mg/dL for women), impaired glucose tolerance (IGT) or diabetes, and truncal obesity. For this study, BMI of 30 kg/m^2 was used as the obesity criterion.

2.3. Statistical analysis

There are no established categorizing criteria to designate insulin resistance. To designate the most insulin-resistant subjects, the index of insulin sensitivity (M'/I) derived at examination 1 was rank ordered. Participants with M'/I values in the lowest tertile at examination 1 were designated *insulin resistant* (IR). These same participants were designated IR at examination 2. Those in the mid and upper tertiles at examination 1 were designated *insulin sensitive* (IS) and also designated IS at examination 2. The differences between the IR and IS groups in age, BMI, BP, lipid profile, and plasma insulin and glucose levels during the OGTT at examination 1 and again at examination 2 were compared using a 2-way analysis of variance (IR vs IS and

male vs female and interaction term) with BMI at the initial examination as a covariate. We also compared longitudinal change within the IR and IS groups for each glucose variable by paired t test. The prevalence of abnormal glucose tolerance, diabetes mellitus, and metabolic syndrome was compared between the IR and IS groups and men vs women using a logistic regression. All continuous measurements are presented as mean ± standard deviation. P values not exceeding .05 were considered statistically significant, and no Bonferroni correction for simultaneous multiple comparisons was applied. All analyses were performed using SAS (Version 8.2, Cary, NC).

3. Results

The study cohort consisted of 114 women and 60 men who were evaluated at the initial examination (examination 1) and reexamined approximately 8 years later (examination 2). Table 1 provides the demographic information on all participants at both examinations 1 and 2. The mean BMI values of all participants, men, and women were in the overweight or obese range at examination 1 and increased further at examination 2. The female participants were more obese than the male participants, with a higher mean BMI at both examinations 1 and 2. The mean systolic and diastolic BPs of all participants, men, and women were comparable at both examinations 1 and 2. The mean systolic BP was higher in male compared with female participants at both examinations 1 and 2. The lipid profiles of all participants, men, and women at examination 1 were comparable with those at examination 2. The mean fasting glucose levels were in the reference range for all subjects, men, and women at examination 1; but the mean fasting glucose was greater than the prediabetic threshold of 100 mg/dL at examination 2. The mean 2-hour OGTT glucose increased substantially from examination 1 to 2.

The relationship between insulin sensitivity measured by insulin clamp at examinations 1 and 2 for each participant showed a significant consistency in insulin sensitivity over 8 years, with a correlation coefficient of $R = 0.51$ ($P < .001$). The subjects were stratified by M'/I tertile based on the results of the insulin clamp procedure at examination 1. The lowest M'/I tertile was designated the IR group and the upper 2 tertiles as the IS group.

The mean values of age, BMI, BP, and lipid profile for the IR and IS groups at examinations 1 and 2 are listed in Table 2. Whereas the mean BMI values of all groups were in the overweight or obese range at examination 1, the mean BMI of the IR group was higher than that of the IS group for men and women at both examinations 1 and 2. The mean systolic and diastolic BPs were also higher in the IR groups than in the IS groups for men and women at both examinations 1 and 2, although the differences became less pronounced at examination 2. The lipid profiles of IS groups appeared more favorable (higher HDL-C and lower triglyceride) than those of IR groups for men and women at both examinations 1 and 2. The LDL-C was significantly higher in the IR men compared with other groups at examination 1, but this difference was no longer significant at examination 2.

Table 3 provides the mean values of plasma insulin and glucose measures for the IR and IS groups during the OGTT at examinations 1 and 2. The measured values for plasma insulin were significantly higher in the IR groups than in the IS groups at both examinations 1 and 2 except for fasting insulin level (insulin 0) at examination 2. When the measured insulin values were normalized by log transformation, there were similarly significant differences between IR and IS groups with somewhat lower (more significant) P values. Glucose measures were also significantly higher in the IR group compared with the IS group at both examinations 1 and 2. Both IR and IS groups had higher glucose measures at examination 2. In longitudinal analysis for change of glucose within each group, there was a statistically significant increase in plasma glucose in both IR and IS groups; however, the increase in each glucose parameter was significantly greater in the IR group. In cross-sectional analysis to compare the change in glucose between IR and IS (men and women) between

Table 1
Demographics of study subjects at examinations 1 and 2

	All subjects (N = 174)		Male (n = 60)		Female (n = 114)	
	Examination 1	Examination 2	Examination 1	Examination 2	Examination 1	Examination 2
Age (y)	32.1 ± 4.0	39.8 ± 3.8	31.3 ± 4.0	39.4 ± 4.0	32.4 ± 4.0	40.0 ± 3.7
BMI (kg/m^2)	30.3 ± 8.2	32.6 ± 8.1	28.2 ± 6.8	30.2 ± 7.2	31.3 ± 8.8	33.9 ± 8.3
SBP (mm Hg)	123 ± 16	128 ± 19	127 ± 15	132 ± 14	121 ± 16	125 ± 21
DBP (mm Hg)	79 ± 13	75 ± 13	80 ± 13	77 ± 12	79 ± 13	73 ± 13
Cholesterol (mg/dL)	178 ± 39	182 ± 37	186 ± 52	183 ± 40	174 ± 30	182 ± 36
HDL-C (mg/dL)	49 ± 18	49 ± 15	48 ± 22	47 ± 15	50 ± 16	50 ± 15
LDL-C (mg/dL)	111 ± 32	117 ± 34	113 ± 38	118 ± 38	109 ± 28	117 ± 32
Triglyceride (mg/dL)	86 ± 46	88 ± 48	101 ± 55	91 ± 52	79 ± 39	87 ± 47
Glucose 0 (mg/dL)	94 ± 12	108 ± 42	97 ± 15	114 ± 52	93 ± 10	104 ± 36
Glucose 120 (mg/dL)	120 ± 33	136 ± 59	114 ± 36	137 ± 67	123 ± 31	135 ± 54

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

Table 2
Body mass index, BP, and lipid profiles of IR and IS groups at examinations 1 and 2

	Male (n = 60)		Female (n = 114)		*P* value		
	IR (n = 20)	IS (n = 40)	IR (n = 38)	IS (n = 76)	Main IR vs IS	Main male vs female	Interaction
Examination 1							
Age (y)	30.9 ± 4.2	31.5 ± 3.9	33.3 ± 4.3	32.0 ± 3.8	.63	.03	.14
BMI (kg/m^2)	34.1 ± 7.1	25.3 ± 4.3	35.8 ± 8.0	29.1 ± 8.1	<.001	.03	.40
SBP (mm Hg)	133 ± 11	124 ± 16	126 ± 15	119 ± 16	.003	.02	.70
DBP (mm Hg)	84 ± 12	78 ± 13	82 ± 15	77 ± 12	.007	.40	.96
Cholesterol (mg/dL)	196 ± 32	181 ± 59	175 ± 33	174 ± 28	.20	.04	.30
HDL-C (mg/dL)	39 ± 8	52 ± 26	45 ± 13	53 ± 16	<.001	.24	.49
LDL-C (mg/dL)	133 ± 29	104 ± 39	114 ± 30	107 ± 26	<.001	.15	.04
Triglyceride (mg/dL)	122 ± 58	90 ± 51	95 ± 53	71 ± 28	<.001	.002	.58
Examination 2							
Age (y)	39.2 ± 4.2	39.6 ± 3.8	40.7 ± 4.2	39.6 ± 3.4	.54	.23	.23
BMI (kg/m^2)	35.3 ± 7.9	27.6 ± 5.2	37.5 ± 8.2	32.1 ± 7.8	<.001	.009	.35
SBP (mm Hg)	137 ± 16	130 ± 13	128 ± 18	124 ± 22	.065	.02	.73
DBP (mm Hg)	80 ± 11	76 ± 13	76 ± 13	72 ± 12	.06	.05	.77
Cholesterol (mg/dL)	191 ± 39	179 ± 40	178 ± 42	184 ± 33	.67	.50	.18
HDL-C (mg/dL)	43 ± 8	49 ± 18	47 ± 16	51 ± 14	.08	.31	.61
LDL-C (mg/dL)	127 ± 37	114 ± 39	113 ± 36	119 ± 30	.51	.44	.10
Triglyceride (mg/dL)	109 ± 70	82 ± 36	93 ± 44	84 ± 48	.04	.43	.26

examinations 1 and 2, the changes in all the glucose measures including fasting glucose, 2-hour glucose on OGTT, and sum glucose on OGTT were significantly greater in the IR than the IS groups. This analysis was adjusted for BMI at examination 1. There were no significant differences between the groups in change (longitudinal or cross sectional) in any lipid parameters or BP from examination 1 to 2.

The mean values of insulin sensitivity derived from the insulin clamp procedure were also provided in Table 3. The difference between IR and IS groups was significant as expected because we defined *insulin resistance* as the lowest tertile of insulin sensitivity adjusted for body fat (M'/I). The difference between IR and IS groups remained significant at examination 2. The mean values of M/I and M'/I were somewhat higher in the IR groups at examination 2, most

Table 3
Insulin and glucose measurements of IR and IS groups at examinations 1 and 2

	Male (n = 60)		Female (n = 114)		*P* value[a]		
	IR (n = 20)	IS (n = 40)	IR (n = 38)	IS (n = 76)	Main IR vs IS	Main male vs female	Interaction
Examination 1							
Insulin 0 (mU/mL)	21.9 ± 21.2	9.0 ± 7.4	16.7 ± 7.6	11.0 ± 9.3	<.001	.62	.25
Sum insulin (mU/mL)	447 ± 213	201 ± 132	482 ± 236	255 ± 159	<.001	.14	.59
Glucose 0 (mg/dL)	104 ± 21.9	93 ± 9	96 ± 11	91 ± 10	<.003	.009	.04
Glucose 120 (mg/dL)	137 ± 37.3	102 ± 29	135 ± 32	117 ± 29	<.001	.74	.05
Sum glucose (mg/dL)	592 ± 112	513 ± 71	550 ± 87	488 ± 81	<.001	.004	.29
M/I[b]	2.79 ± 1.00	11.01 ± 4.75	2.54 ± 0.73	9.41 ± 5.57	<.001	.21	.36
M'/I[c]	3.78 ± 1.25	13.50 ± 5.05	3.94 ± 1.15	13.66 ± 7.42	<.001	.86	1.00
Examination 2							
Insulin 0 (mU/mL)	14.7 ± 8.2	9.0 ± 6.0	15.9 ± 13.0	12.1 ± 14.5	.21	.47	.76
Sum insulin (mU/mL)	278 ± 111	190 ± 154	314 ± 180	231 ± 150	.005	.16	.93
Glucose 0 (mg/dL)	136 ± 84	103 ± 20	111 ± 43	101 ± 31	.006	.06	.10
Change in glucose 0 (mg/dL)	32 ± 65	11 ± 16	15 ± 43	10 ± 32	.05	.28	.30
Glucose 120 (mg/dL)	173 ± 91	121 ± 47	156 ± 82	125 ± 30	<.001	.52	.30
Change in glucose 120 (mg/dL)	37 ± 74	19 ± 43	26 ± 80	7 ± 33	.05	.29	.92
Sum glucose (mg/dL)	699 ± 255	560 ± 126	631 ± 259	527 ± 90	<.001	.10	.56
Change in sum glucose (mg/dL)	123 ± 219	47 ± 95	96 ± 248	38 ± 91	.01	.65	.65
M/I[b]	4.85 ± 2.99	11.74 ± 7.23	4.48 ± 3.13	8.48 ± 5.06	<.001	.06	.13
M'/I[c] (mg/[kg min] × 100)	6.94 ± 3.65	14.89 ± 8.46	7.43 ± 4.98	13.47 ± 7.31	<.001	.71	.45

[a] All *P* values represent adjustment for BMI at examination 1.
[b] M/I = milligrams per kilogram per minute divided by steady-state insulin concentration ×100.
[c] M'/I = milligrams per kilogram of fat-free mass per minute divided by steady-state insulin concentration ×100.

likely because the insulin clamp procedure was not done on subjects who developed clinical diabetes and were receiving treatment by examination 2.

There was a significantly higher percentage of subjects with metabolic syndrome, abnormal glucose tolerance, and diabetes mellitus in the IR groups than in the IS groups at both examinations 1 and 2, as shown in Table 4. With regard to metabolic syndrome, 50.0% of IR men and 47.4% of IR women at examination 1 and 55.0% of IR men and 58.3% IR women at examination 2 met the ATP III definition for metabolic syndrome, compared with only 12.5% of IS men and 18.4% of IS women at examination 1 and 21.6% of IS men and 26.3% of IS women at examination 2. Of note, 3 subjects in the male IS group and 2 subjects in the female IR group were missing lipid data; and it was not possible to determine their metabolic syndrome status. The prevalence of abnormal glucose tolerance was substantially higher in the IR groups compared with IS groups at examination 1, and the difference remained significant at examination 2. Although known diabetes was an examination 1 exclusion criteria, previously undetected diabetes was identified in some participants at examination 1 based on the results of the OGTT data. In the IR group, 10% of the men and 5.3% of the women met the ADA criteria for diabetes, with none detected in the IS group at examination 1. At examination 2, 25% of IR men and 13.5% of IR women met the ADA criteria for diabetes compared with 7.5% of IS men and 2.6% of IS women.

4. Discussion

This longitudinal study of healthy young African American adults demonstrated that insulin resistance, as determined by insulin clamp, is strongly associated with metabolic syndrome and heightened risk for deterioration in glucose tolerance. The *IR groups*, defined as the lowest tertile of insulin sensitivity measured by insulin clamp, had greater increase in fasting and 2-hour OGTT glucose levels and higher percentage of subjects with abnormal glucose tolerance and diabetes mellitus than the IS groups over the 8 years of follow-up. With regard to cardiovascular risk factors, the IR groups tended to have higher BPs and less favorable lipid profiles than the IS groups over the 8 years of follow-up.

Insulin resistance has been previously shown to increase the risk for development of type 2 diabetes mellitus in other ethnic groups. In a prospective study of 200 healthy nondiabetic young Pima Indian adults over an average follow-up of 5.3 years, Lillioja et al [15] reported that insulin resistance, measured by insulin clamp, predicted a high risk of developing type 2 diabetes mellitus, with a relative hazard ratio of 30.8. In a later study of 254 Pima Indians with NGT and 145 Pima Indians with IGT, insulin resistance, measured by insulin clamp, predicted an increased risk of progressing from NGT to IGT and also from IGT to type 2 diabetes mellitus during an average follow-up of 4 to 5 years. These investigators defined *insulin resistance* as clamp value less than the median [16]. Other studies have used various surrogate indicators of insulin resistance to predict the risk of developing diabetes. Insulin resistance was assessed by fasting plasma insulin concentration in a study of 714 initially nondiabetic Mexican Americans by Haffner et al [17]. The cohort was stratified by insulin quartiles, and data showed that increasing plasma insulin concentration predicted a progressively increasing risk of developing type 2 diabetes mellitus over 7 years, with relative risk of 1, 1.5, 2, and 3.7 when moving from the lowest insulin quartile to the highest insulin quartile. Using insulin resistance estimated by homeostasis model (HOMA-IR), the same group of investigators showed that HOMA-IR predicted type 2 diabetes mellitus in the 3.5 years of follow-up in the Mexico City Diabetes Study, a population-based study of diabetes and cardiovascular risk factors involving 1449 subjects [18]. In the Strong Heart Study of 12 283 nondiabetic Native Americans, Resnick et al [19] reported that HOMA-IR predicted increased risk of diabetes over the mean follow-up of 7.6 years. In a study on 155 normoglycemic offspring, with both parents having type 2 diabetes mellitus, Martin et al [20] reported that low insulin sensitivity contributed to a heightened risk of developing diabetes over 6 to 25 years.

Table 4
Percentage of subjects with metabolic syndrome, abnormal glucose tolerance, and diabetes mellitus in IR and IS groups at examinations 1 and 2

	Male (total n = 60)		Female (total n = 114)		*P* value	
	IR (total n = 20)	IS (total n = 40)	IR (total n = 38)	IS (total n = 76)	IR vs IS	Male vs female
	% (n)	% (n)	% (n)	% (n)		
Examination 1						
Metabolic syndrome	50.0 (10)	12.5 (5)	47.4 (18)	18.4 (14)	<.001	.65
Abnormal glucose tolerance	35.0 (7)	17.5 (7)	50.0 (19)	27.6 (21)	.006	.11
Diabetes mellitus	10.0 (2)	0 (0)	5.3 (2)	0 (0)	.96	.51
Examination 2						
Metabolic syndrome	55.0 (11)	21.6 (8)	58.3 (21)	26.3 (20)	<.001	.57
Abnormal glucose tolerance	80.0 (16)	32.5 (13)	57.9 (22)	39.5 (30)	<.001	.72
Diabetes mellitus	25.0 (5)	7.5 (3)	13.5 (5)	2.6 (2)	.007	.12

Although African Americans have high rates of type 2 diabetes mellitus, limited longitudinal data are available on this ethnic group. Osei et al [21-23] conducted extensive studies on metabolic risk factors in African Americans including offspring of diabetic parents. In a prospective study of 81 prediabetic African Americans who were the first-degree relatives of individuals with type 2 diabetes mellitus, these investigators demonstrated that HOMA-IR predicted an increased risk of developing diabetes over a median follow-up of 6 years [24]. Using insulin clamp procedure to quantify insulin sensitivity, our study on 174 nondiabetic African Americans over 8 years is consistent with the previous report by Osei and colleagues.

Insulin resistance and hyperinsulinemia are linked to hypertension and cardiovascular disease. In a study of 147 healthy nonobese volunteers whose insulin sensitivity was measured by insulin suppression test, Yip et al [25] showed that, over approximately 5 years of follow-up, 18.5% of subjects in the most insulin-resistant tertile developed hypertension and cardiovascular disease including coronary artery disease, stroke, or peripheral vascular disease, whereas only 8.2% of subjects in the mid tertile and none in the lowest tertile developed clinical evidence of cardiovascular disease. In a subsequent expanded study of 208 healthy nonobese volunteers, the same investigators demonstrated that 36% of subjects in the most insulin-resistant tertile developed cardiovascular events, diabetes, and cancer, whereas none in the most insulin-sensitive tertile developed these disorders, during an average follow-up of 6 years [26]. Using data from a cohort of African Americans followed for over 28 years since birth, Hulman et al [27] reported that faster growth during early childhood and obesity increases the risk of insulin resistance and cardiovascular disease in adulthood. In the San Antonio Heart Study, a population-based prospective study of 2569 Mexican and white Americans conducted over a median follow-up of 7.5 years, there was a significant association between HOMA-IR and cardiovascular disease outcomes [28]. In a population-based Danish study of 2493 men and women over a median follow-up of 9.4 years, HOMA-IR was an independent predictor of incident cardiovascular disease [29]. Interestingly, data from the Insulin Resistance Atherosclerosis Study showed that higher insulin sensitivity estimated by the minimal model of Bergman is associated with less atherosclerosis in Hispanics and whites but not in blacks [30]. A Japanese study of 145 normotensive subjects over 3 years of follow-up reported that insulin resistance is associated with subsequent development of hypertension [31].

Chen et al [32] analyzed data from the Bogalusa Heart Study to estimate the longitudinal benefit of a very low risk profile. These investigators showed that low risk levels of metabolic syndrome parameters were associated with lower measures of cardiovascular risk in adulthood. Based on data from the Framingham Offspring study on 2898 people without diabetes or cardiovascular disease at baseline, HOMA-IR failed to independently predict incident cardiovascular disease [33]. Our data showed that the IR groups had higher BPs than the IS groups at both examinations 1 and 2. However, the BP differences between the IR and IS groups were dampened at examination 2, as many study subjects started antihypertensive medications. Although the IR groups had less favorable lipid profiles than the IS groups at examination 1, the differences became statistically insignificant at examination 2 with little known use of lipid-lowering agents. We have previously shown, from data on young adult African Americans, that there is a significant association of both triglyceride and HDL-C with insulin resistance. Despite the association between insulin resistance and triglyceride, only 10% of the study population had elevated triglyceride according to the ATP III criteria for metabolic syndrome [34].

Although this study was limited to 174 subjects, it is the largest longitudinal study of nondiabetic African Americans conducted to examine the relationship of insulin resistance with subsequent deterioration in glucose tolerance over a period of 8 years. Our data showed a significant difference in BMI between the IR and IS groups, which could certainly confound the predictive value of insulin resistance in developing abnormal glucose tolerance and diabetes. However, after adjusting for the BMI at examination 1, the predictive value of insulin resistance for deterioration of glucose tolerance remains significant. In our analysis for changes in associated risk factors, we were unable to detect significant changes in BP or plasma lipid levels. It is likely that BP changes were to some extent confounded by the addition of antihypertensive medications in participants who began treatment of hypertension between examinations 1 and 2. Although very few participants were receiving statin therapy at examination 2, the laboratory that performed the lipid assays changed between examinations 1 and 2. It is possible that subtle changes in laboratory results could have impaired our capacity to detect significant longitudinal change in the lipid variables in this sample size.

In conclusion, our study examined longitudinally the relationship of insulin resistance determined by insulin clamp and the risk of developing abnormal glucose tolerance and diabetes in 174 nondiabetic young African American adults over a period of 8 years. The data demonstrated that insulin resistance predicts deterioration in glucose tolerance and increased risk of developing diabetes mellitus.

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References

[1] Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the US population: National Health And Nutrition Examination Survey 1999-2002. Diabetes Care 2006;29:1263-8.

[2] Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001; 24:683-9.

[3] Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003;52:1210-4.

[4] Ferrannini E. Insulin resistance versus insulin deficiency in non–insulin-dependent diabetes mellitus: problems and prospects. Endocr Rev 1998;19:477-90.

[5] Haffner SM. Insulin resistance, inflammation, and the prediabetic state. Am J Cardiol 2003;92:18J-26J.

[6] DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:E214-23.

[7] Womersley J. A comparison of the skinfold method with extent of "overweight" and various weight-height relationships in the assessment of obesity. Br J Nutr 1977;38:271-84.

[8] Heymsfield SB, McManus C, Stevens V, Smith J. Muscle mass: reliable indicator of protein-energy malnutrition severity and outcome. Am J Clin Nutr 1982;35:1192-9.

[9] Rizza RA, Mandarino LJ, Gerich JE. Dose-response characteristics for effects of insulin on production and utilization of glucose in man. Am J Physiol 1981;240:E630-9.

[10] Falkner B, Kushner H, Tulenko T, Sumner AE, Marsh JB. Insulin sensitivity, lipids, and blood pressure in young American blacks. Arterioscler Thromb Vasc Biol 1995;15:1798-804.

[11] Bachorik PS, Walkner RE, Virgil DG. High-density-lipoprotein cholesterol in heparin-$MnCl_2$ supernates determined with the Dow enzymic method after precipitation of Mn^{2+} with HCO_3^-. Clin Chem 1984;30:839-42.

[12] Friedwald WT, Levy RI, Frederickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.

[13] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2006;29:S43-8.

[14] Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults. (Adult Treatment Panel III). JAMA 2001;285:2486-97.

[15] Lillioja S, Mott DM, Spraul M, et al. Insulin resistance and insulin secretary dysfunction as precursors of non–insulin-dependent diabetes mellitus: prospective studies of Pima Indians. N Engl J Med 1993;329: 1988-92.

[16] Weyer C, Tataranni PA, Bogardus C, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. Diabetes Care 2000;24:89-94.

[17] Haffner SM, Miettinen H, Gaskill SP, Stern MP. Decreased insulin secretion and increased insulin resistance are independently related to the 7-year risk of NIDDM in Mexican-Americans. Diabetes 1995;44: 1386-91.

[18] Haffner SM, Gonzalez C, Miettinen H, et al. A prospective analysis of the HOMA model: the Mexico City Diabetes Study. Diabetes Care 1996;19:1138-41.

[19] Renick HE, Jones K, Ruotolo G, et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic American Indians: the Strong Heart Study. Diabetes Care 2003;26: 861-7.

[20] Martin BC, Warram JH, Krolewski AS, et al. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow up study. Lancet 1992;340:925-9.

[21] Osei K, Cottrell DA, Harris B. Differences in basal and post-stimulation glucose homeostasis in nondiabetic first-degree relatives of black and white patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 1992;75:82-6.

[22] Osei K, Cottrell DA. Minimal model analyses of insulin sensitivity and glucose dependent glucose disposal in black and white Americans: a study of persons at risk for type 2 diabetes. Eur J Clin Invest 1994;24: 843-50.

[23] Osei K, Gaillard T, Schuster DID. Pathogenetic mechanism of impaired glucose tolerance and type 2 diabetes in African Americans: the significance of insulin secretion, insulin sensitivity and glucose effectiveness. Diabetes Care 1997;20:396-404.

[24] Osei K, Rhinesmith S, Gaillard T, Schuster D. Impaired insulin sensitivity, insulin secretion, and glucose effectiveness predict future development of impaired glucose tolerance and type 2 diabetes in pre-diabetic African Americans: implication for primary diabetes prevention. Diabetes Care 2004;27:1439-46.

[25] Yip J, Facchini FS, Reaven GM. Resistance to insulin-mediated glucose disposal as a predictor of cardiovascular disease. J Clin Endocrinol Metab 1998;83:2773-6.

[26] Facchini FS, Hua N, Abbasi F, Reaven GM. Insulin resistance as a predictor of age-related diseases. J Clin Endocrinol Metab 2001;86: 3574-8.

[27] Hulman S, Kushner H, Katz S, Falkner B. Can cardiovascular risk be predicted by newborn, childhood, and adolescent body size? An examination of longitudinal data in urban African Americans. J Pediatr 1998;132:90-7.

[28] Hanley AJG, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. Diabetes Care 2002;25:1177-84.

[29] Jeppesen J, Hansen TW, Rasmussen S, et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease. J Am Coll Cardiol 2007;49:2112-9.

[30] Howard G, O'Leary DH, Zaccaro D, et al. Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. Circulation 1996;93:1809-17.

[31] Kashiwabara H, Inaba M, Maruno Y, et al. Insulin levels during fasting and the glucose tolerance test and Homa's index predict subsequent development of hypertension. J Hypertens 2000;18:83-8.

[32] Chen W, Srinivasan SR, Li S, et al. Metabolic syndrome variables at low levels in childhood are beneficially associated with adulthood cardiovascular risk. Diabetes Care 2005;28:138-43.

[33] Rutter MK, Meigs JB, Sullivan LM, et al. Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study. Diabetes 2005;54:3252-7.

[34] Stein E, Kushner H, Gidding S, Falkner B. Plasma lipid concentrations in nondiabetic African American adults: associations with insulin resistance and the metabolic syndrome. Metabolism 2007;56:954-60.