Do Blacks With NIDDM Have an Insulin-Resistance Syndrome?

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NIDDM has been postulated to be a component of a more generalized metabolic syndrome, Syndrome X, caused by insulin resistance. Although the components of the syndrome include glucose intolerance, hypertension, increased TG, and decreased HDL cholesterol, their relationship to insulin resistance and/or hyperinsulinemia is controversial. Recent investigations have shown racial differences in the relationship between insulin resistance and BP in nondiabetic populations. We assessed the relationship between insulin resistance and the other components of the syndrome in 37 black men and 53 black women with NIDDM. Insulin sensitivity was determined by measuring glucose disposal with the euglycemic insulin clamp technique with a 1 mU · kg^{-1} · min^{-1} insulin infusion. We also determined fasting lipid profiles and BP. In this group of black men and women with NIDDM, 30% were insulin sensitive, and 70% were insulin resistant. No correlation existed between insulin sensitivity and sBP or dBP in either sex. Fasting serum TGs were inversely correlated with insulin sensitivity for both men ($r = -0.401$, $P = 0.02$) and women ($r = -0.366$, $P = 0.008$). Serum HDL cholesterol was highly correlated with insulin sensitivity for men ($r = 0.421$, $P = 0.01$) but not for women ($r = 0.071$, $P = 0.62$). Fasting serum TG levels and serum HDL-cholesterol levels were highly correlated in an inverse relationship in men ($r = -0.368$, $P = 0.03$), but not women ($r = -0.199$, $P = 0.17$). In summary, BP does not correlate with insulin resistance in blacks with NIDDM. Normal insulin sensitivity occurs in 33% of black men and 25% of black women with NIDDM. In black women with NIDDM, serum HDL cholesterol does not correlate with either insulin sensitivity or fasting serum TGs. The data fail to support a major association of insulin resistance with metabolic abnormalities in black women with NIDDM and show only a weak association in black men with NIDDM. *Diabetes* 42:444–49, 1993

The concept that NIDDM is one component of a more generalized metabolic syndrome caused by insulin resistance and/or hyperinsulinemia has received considerable support (1–3). Resistance to insulin-stimulated glucose uptake is associated with hyperinsulinemia, glucose intolerance and, eventually diabetes, increased VLDL TG, and decreased HDL-cholesterol concentrations. The controversy concerning this syndrome has been about whether hypertension is part of the syndrome and what relationship if any exists between hypertension and insulin resistance and/or hyperinsulinemia. Investigators have shown racial differences exist in the relationship between insulin resistance and BP in nondiabetic populations (4). Specifically, a positive relationship appears to exist in white populations.

We previously have reported that many blacks with NIDDM do not have insulin resistance (5,6). These data in conjunction with the reported lack of relationship between insulin resistance and BP in nondiabetic obese blacks suggested the components of Syndrome X, or the generalized metabolic syndrome, may have different relationships in blacks than those observed in whites. This study describes the relationships among insulin

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NIDDM, non-insulin-dependent diabetes mellitus; TG, triglyceride; HDL, high-density lipoprotein; BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure; VLDL, very-low-density lipoprotein; BMI, body mass index; HGP, hepatic glucose production; R_a, rate of glucose appearance; R_d, rate of glucose disappearance; RIA, radioimmunoassay; LDL, low-density lipoprotein; CV, coefficient of variation; CDC, Centers for Disease Control; HPLC, high-performance liquid chromatography; FPG, fasting plasma glucose; CAD, coronary artery disease; IDDM, insulin-dependent diabetes mellitus; DKA, diabetic ketoacidosis; HLA, human leukocyte antigen; OHA, oral hypoglycemic agent.

sensitivity, sBP and dBP, fasting serum TG, and HDL-cholesterol levels in 90 blacks with NIDDM.

RESEARCH DESIGN AND METHODS

We studied 37 black men and 53 black women with NIDDM, ranging from 28 to 65 yr of age. Their ethnic origins were distributed equally among American-born and Caribbean-born blacks. BMI (kg/m^2) ranged from 20.4 to 42.1 kg/m^2. NIDDM had been diagnosed based on age of diagnosis, clinical course, and response to therapy. Of the 90 patients, 13 were being treated with insulin, 31 with diet alone, 43 with oral sulfonylurea agents, and 3 with oral sulfonylurea agents and insulin in combination.

All patients were instructed in an appropriate American Diabetes Association diet, and their body weights had not changed significantly during the several months preceding the study. No individual had a history of significant hepatic, renal, or endocrine disease. The patients were selected from our Diabetes Clinic and were studied at the General Clinical Research Center at the State University of New York-Health Science Center at Brooklyn after written informed consent was obtained.

BP was taken twice in the morning in the sitting position on 3 days with an appropriately sized mercury sphygmomanometer. We measured sBP and dBP at the time of the first and fifth Korotkoff sounds, respectively. The average of the measurements was used as the BP value. Insulin sensitivity and HGP were determined by a modification of the euglycemic insulin clamp technique (7) after an overnight fast. Diabetic medication was withheld on the morning of the study.

A catheter was placed in the antecubital vein antegrade for the administration of infusates. A catheter was placed retrograde in the hand, which was kept in a warming box at 68°C to provide arterialized venous blood for sampling. We infused [3-^{3}H]D-glucose in a primed continuous manner for 180–210 min before the start of the insulin infusion; 236 nCi/kg [3-^{3}H]D-glucose was injected as a bolus, followed by a continuous infusion at 2.36 nCi · kg^{-1} · min^{-1}. After the equilibration period, soluble human insulin was infused initially as a priming dose to raise the plasma insulin acutely to the desired level (8), and then was infused at a rate of 1.0 mU · kg^{-1} · min^{-1} for 120 min. Plasma glucose was measured every 5 min and was clamped at 5.5 mM with a variable glucose infusion (6).

We took blood samples every 15 min for hormone measurements and specific activity of [3-^{3}H]D-glucose during the insulin infusions. Urine was assayed for glucose losses throughout the study, and basal and insulin-stimulated glucose disposal rates were corrected for these losses.

HGP. R_a and R_d were measured in the basal state and during the last 60 min of the insulin-infusion period. Before basal measurements were taken, [3-^{3}H]D-glucose was infused for at least 180–210 min. Because plasma counts per minute were stable in multiple samples taken every 10 min for the 40 min before the start of the insulin infusion, we assumed steady state had been reached. Thus, HGP in the basal state was calculated on the basis of steady-state kinetics. We used Steele's equations to calculate R_a and R_d during the insulin-infusion period (9). HGP is equal to the total R_a minus the rate of exogenously administered glucose.

TABLE 1
Clinical characteristics of the study subjects

	Men	Women	*P*
Number	37	53	
Age (yr)	44.9 ± 1.6	50.2 ± 1.2	<0.01
BMI (kg/m2)	26.8 ± 0.5	29.7 ± 0.6	<0.005
FPG (mM)	7.0 ± 0.4	8.6 ± 0.5	<0.02
Glucose disposal (mg · kg^{-1} · min^{-1})	4.58 ± 0.35	4.11 ± 0.27	NS
sBP (mmHg)	122 ± 2	133 ± 3	<0.025
dBP (mmHg)	80 ± 2	85 ± 1	<0.05
Cholesterol (mM)	4.96 ± 0.20	5.40 ± 0.17	NS
TG (mM)	1.25 ± 0.92	1.10 ± 0.07	NS
HDL cholesterol (mM)	1.08 ± 0.05	1.39 ± 0.05	<0.001
LDL cholesterol (mM)	3.29 ± 0.20	3.50 ± 0.17	NS

Data are means ± SE.

Insulin sensitivity. Total glucose disposal in the presence of a constant infusion of insulin at 1 mU · kg^{-1} ·min^{-1} was defined as the sum of the rate of HGP and the exogenously infused glucose. We calculated urinary glucose losses for each insulin-infusion period and subtracted as appropriate.

Plasma glucose was measured by the glucose oxidase method with a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA). Specific activity for [3-^{3}H]D-glucose was determined on plasma samples deproteinized with barium hydroxide and zinc sulfate. A standard double antibody RIA assayed plasma insulin levels(10). Serum lipids were measured after a 12-h fast. Total serum cholesterol and serum TG were measured enzymatically with the Kodak Ektachem 400 system (Rochester, NY) (11,12). Serum HDL cholesterol was similarly measured enzymatically after the removal of LDL and VLDL using dextran magnesium precipitation (13). The interassay CVs for total cholesterol and TG were 2.6 and 3.0%, whereas that for HDL cholesterol was 4.8%.

The College of American Pathology provided control sera. All lipid assays met the CDC and College of American Pathology Standardization programs. Serum LDL cholesterol was estimated according to Friedewald (14)—i.e., serum LDL cholesterol = serum total cholesterol − (serum HDL cholesterol + 0.2 × serum TG).

Statistical analyses. For statistical analyses, we used Student's *t* test and simple and multiple linear regression analysis (15). Data are presented as means ± SE or means ± SD.

Materials. We purchased [3-^{3}H]D-glucose (13.5 Ci. mmole^{-1}) from New England Nuclear Company (Boston, MA). HPLC confirmed 98% purity. Eli Lilly (Indianapolis, IN) kindly provided regular human insulin.

RESULTS

Table 1 describes the characteristics of the study group. The women were significantly older, more obese, and

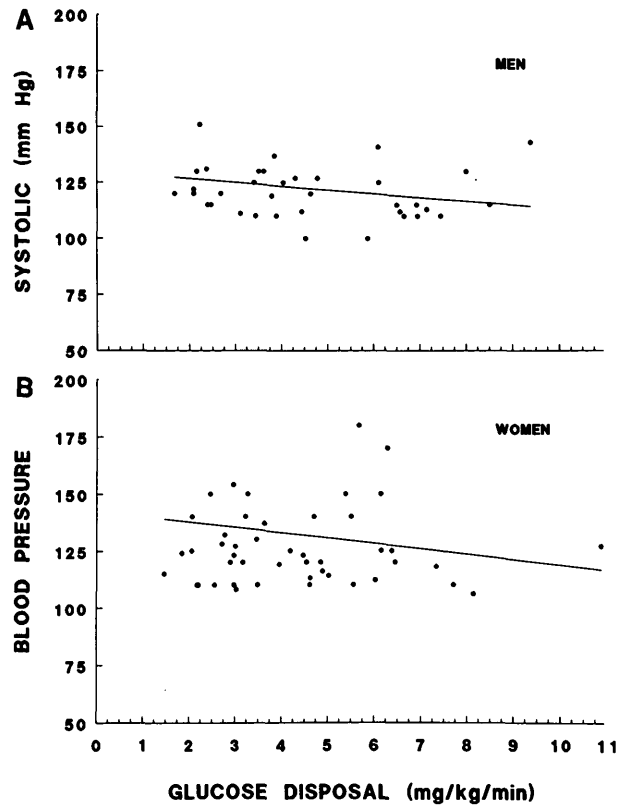

FIG. 1. Correlation between insulin sensitivity (glucose disposal) and sBP in black men and women with NIDDM. *A*: In men, $r = -0.124$, $P = 0.47$. *B*: In women, $r = -0.017$, $P = 0.91$. Glucose disposal of 1.0–11.0 mg · kg^{-1} · min^{-1} is equal to 5.56–61.11 uM · kg^{-1} · min^{-1}.

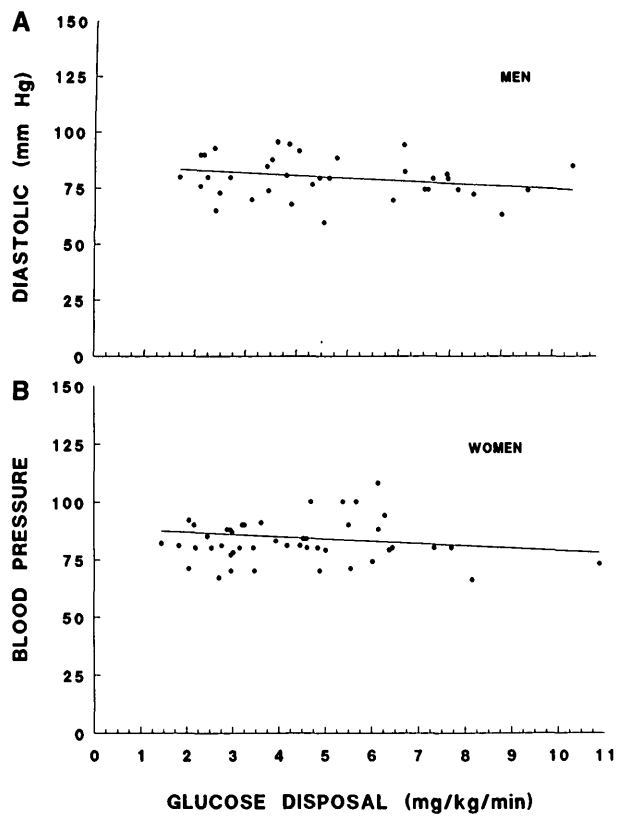

FIG. 2. Correlation between insulin sensitivity (glucose disposal) and dBP in black men and women with NIDDM. *A*: In men, $r = -0.169$, $P = 0.32$. *B*: In women, $r = -0.067$, $P = 0.66$. Glucose disposal of 1.0–11.0 mg · kg^{-1} · min^{-1} is equal to 5.56–61.11 uM · kg^{-1} · min^{-1}.

had higher FPG than the men. Their mean sBP and dBP also were higher, as was their mean serum HDL-cholesterol level. Both men and women were in reasonable glycemic control as reflected by their mean FPG levels of 7.0 ± 0.4 and 8.6 ± 0.5 mM, respectively. Seven women and one man were on antihypertensive medications at the time of the study.

Figure 1 illustrates the lack of a significant relationship between sBP and insulin sensitivity as estimated by glucose disposal in response to a 1 mU · kg^{-1} · min^{-1} insulin infusion in the 36 black men ($r = -0.124$, $P = 0.47$) and the 46 black women ($r = -0.017$, $P = 0.91$) who were not on antihypertensive therapy. Figure 2 shows a similar lack of relationship between dBP and insulin sensitivity in these same black men ($r = -0.169$, $P = 0.32$) and women ($r = -0.067$, $P = 0.66$).

Insulin sensitivity as estimated by glucose disposal in response to a 1 mU · kg^{-1} · min^{-1} insulin infusion was significantly inversely correlated with fasting serum TG levels in both black men ($r = -0.401$, $P = 0.02$) and women ($r = -0.366$, $P = 0.008$), as shown in Fig. 3. Glucose disposal in 13 of 37 (35%) men and 14 of 53 (26%) women was ≥5.5 mg · kg^{-1} · min^{-1} (30.55 uM · kg^{-1} · min^{-1}). All of them had a fasting serum TG <1.41 mM. In contrast, 12 of 23 (52%) men and 12 of 38 (32%) women with glucose disposals <5.5 mg · kg^{-1} · min^{-1} (30.55 uM · kg^{-1} · min^{-1}) had fasting serum TG levels >1.41 mM. Glucose disposal of 5.5 mg · kg^{-1} · min^{-1} (30.55 uM · kg^{-1} · min^{-1}) is the mean − 2 SD of our healthy, black, nondiabetic control subjects ($n = 9$; BMI, 25.2 ± 2.9 kg/m^2; glucose disposal, 7.59 ± 1.01 mg · kg^{-1} · min^{-1} [42.17 ± 5.61 uM · kg^{-1} · min^{-1}]).

The relationship of serum HDL cholesterol to insulin sensitivity differed depending on sex. As shown in Fig. 4, men exhibited a significant positive correlation ($r = 0.421$, $P = 0.01$), but women did not ($r = 0.071$, $P = 0.62$). Whereas 15 of 36 (42%) men had serum HDL-cholesterol levels <1.0 mM, only 2 of 50 (4%) women did.

Most studies have shown or implied that fasting serum TG levels and serum HDL-cholesterol levels have a tightly coupled inverse relationship. Figure 5 shows this also is true for black men with NIDDM ($r = -0.368$, $P = 0.03$). As also seen in Fig. 5, however, no significant simple correlation exists between fasting serum TGs and serum HDL cholesterol in black women with NIDDM ($r = -0.199$, $P = 0.17$).

To estimate the influence of BMI, we did multiple regression analysis of the data with glucose disposal and BMI as independent variables. Table 2 shows multiple R and the partial correlations for glucose disposal and BMI. BMI was significantly correlated only with dBP in men. The partial correlation of BMI in men was 0.450 ($P = 0.007$) for dBP and there was no correlation with glucose disposal (partial correlation −0.040, $P = 0.82$).

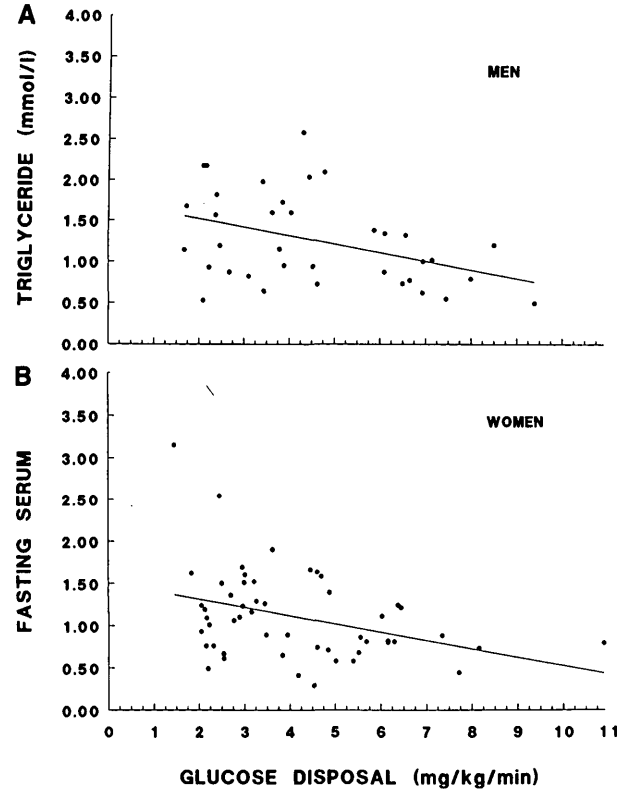

FIG. 3. Correlation between insulin sensitivity (glucose disposal) and fasting serum TGs in black men and women with NIDDM. *A*: In men, $r = -0.401$, $P = 0.02$. *B*: In women, $r = -0.366$, $P = 0.008$. Glucose disposal of 1.0–11.0 mg · kg^{-1} · min^{-1} is equal to 5.56–61.11 uM · kg^{-1} · min^{-1}.

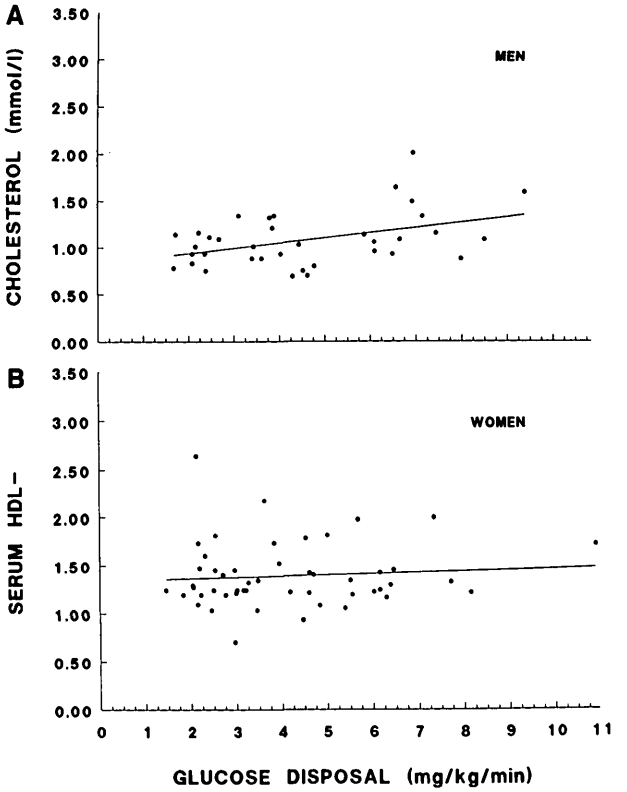

FIG. 4. Correlation between insulin sensitivity (glucose disposal) and serum HDL-cholesterol levels in black men and women with NIDDM. *A*: In men, $r = 0.421$, $P = 0.01$. *B*: In women, $r = 0.071$, $P = 0.62$. Glucose disposal of 1.0–11.0 mg · kg^{-1} · min^{-1} is equal to 5.56–61.11 uM · kg^{-1} · min^{-1}.

We performed multiple regression analysis with the dependent variable of serum TG and the independent variables of serum HDL cholesterol and BMI in men and women (data not shown). In men, the multiple *R* was 0.430 ($P = 0.035$). Serum HDL cholesterol showed a partial correlation of −0.293 ($P = 0.07$). BMI had no influence on this inverse relationship between serum TG and serum HDL cholesterol as the partial correlation was 0.222 ($P = 0.17$). In women, however, BMI significantly affected this relationship. Multiple *R* was 0.405 ($P = 0.01$). BMI had a partial correlation of 0.360 ($P = 0.01$) and was greater than the partial correlation of serum HDL cholesterol ($r = -0.256$, $P = 0.06$).

Because the group of women studied were older than the men, we determined whether age had any influence on the relationships studied in each sex by performing multiple regression analysis incorporating age as an independent variable. Though the partial correlation for age was significant for sBP in women ($r = -0.363$, $P = 0.02$), it did not change the results, showing a lack of relationship between sBP and insulin sensitivity in this group of women. Age had no influence on sBP in men nor any influence on dBP, serum TGs, and serum HDL cholesterol in either men or women. The partial correlations were not significant in all analyses.

DISCUSSION

Some researchers have proposed that insulin resistance and/or hyperinsulinemia are associated with the development of glucose intolerance, increased VLDL TG, decreased HDL cholesterol, and hypertension (1). They postulate that these metabolic abnormalities are part of a more generalized syndrome, Syndrome X, and are the link to increased CAD noted in patients with NIDDM.

Our data indicate the following: *1*) normal insulin sensitivity, not insulin resistance, is present in ~33% of black men and 25% of black women with NIDDM; *2*) BP in black men and women with NIDDM is not significantly correlated with insulin resistance; and *3*) serum HDL cholesterol in black women is independent of insulin sensitivity and is not inversely correlated with fasting serum TGs in a simple correlation. These data do not support a major association of insulin resistance with metabolic abnormalities in black patients with NIDDM.

We previously have described the existence of an insulin-sensitive black population with NIDDM. We have shown that this population is not a slowly developing IDDM population based on the following features: *1*) onset of diabetes after 30 yr of age; *2*) absence of frequent episodes of DKA; *3*) absence of serum anti-islet cell antibodies; *4*) maintenance of some, though inadequate, insulin secretion; *5*) lack of an association with HLA DR3/DR4 histocompatibility antigens; and *6*) long-term therapeutic response to diet and/or OHAs in most patients (5,6,16–18).

The relationship of the various components of Syndrome X and CAD to insulin resistance and/or hyperinsulinemia in different racial populations is quite variable

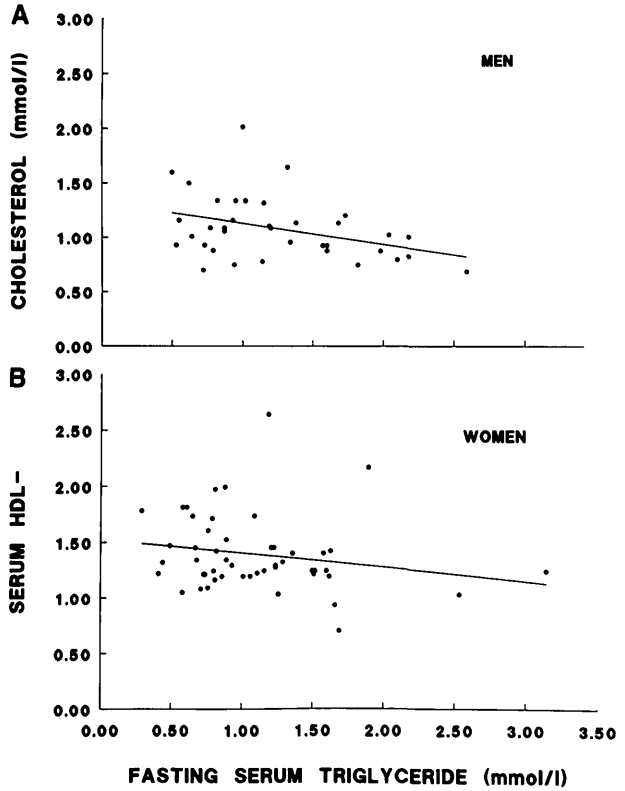

FIG. 5. Correlation between fasting serum TG and serum HDL-cholesterol levels in black men and women with NIDDM. *A*: In men, $r = -0.368$, $P = 0.03$. *B*: In women, $r = -0.199$, $P = 0.17$.

and raises considerable questions about its significance (4,19,20). Of particular concern are questions relating the pathogenesis of some forms of essential hypertension, increased CAD prevalence, and abnormal serum lipid and lipoprotein metabolism to insulin resistance and/or hyperinsulinemia.

Numerous investigators have evaluated, with varying results, the relationship of hypertension to insulin resistance in nondiabetic groups. With the euglycemic clamp, Ferrannini et al. (21) showed insulin resistance in 13 young, lean, nondiabetic hypertensive white men, and Falkner (22) obtained similar results in young, nondiabetic black men with borderline hypertension. Yet in a Finnish NIDDM population, Laasko et al. (23) suggested hypertension and insulin resistance interplay only in the nonobese subgroup.

Another study showed the relationship between BP and insulin sensitivity in the nondiabetic population differs among racial groups. In their study of obese whites, blacks, and Pima Indians of both sexes, Saad et al. (4) found BP was significantly correlated with insulin resistance only for the white population. Data from a study of three Pacific Island populations with a high prevalence of NIDDM and obesity, as well as that from three ethnic populations in Mauritius, showed little or no relationship between fasting and oral glucose-stimulated insulin levels and BP (24,25). Anderson et al. (26) evaluated changes in BP in response to insulin infusions in young, lean, nondiabetic men. Acute increases of plasma insulin within the physiological range caused forearm vasodilatation and did not result in an increase in BP.

In studying 247 healthy, normotensive, nonobese, nondiabetic Italian male factory workers, Zavaroni et al. (27) found that hyperinsulinemia was associated with higher sBP, dBP, and fasting plasma TG levels and lower plasma HDL-cholesterol levels. They concluded that healthy individuals with hyperinsulinemia and normal glucose tolerance have an increase in risk factors for CAD. In the 15-yr follow-up of 6903 men in the Paris Prospective Study, plasma insulin level 2 h after oral glucose, but not fasting plasma insulin level, was an independent risk factor for death from CAD (28).

Other studies, however, have shown that despite marked hyperinsulinemia and severe insulin resistance, the Pima Indians have a low prevalence of CAD, suggesting no linkage exists between insulin resistance and macrovascular disease in this population (19). A study of Mexican-American men with NIDDM shows similar discordance between insulin resistance and hyperinsulinemia and the death rate from CAD (20). Thus, the relationship, if any, between insulin resistance and/or hyperinsulinemia and CAD is not a simple one.

Previous investigators have shown that in populations susceptible to NIDDM, increased VLDL TG and reduced HDL cholesterol are seen before the development of hyperglycemia as well as being influenced by subsequent hyperglycemia (29). In the study of nondiabetic Pima Indians, fasting plasma TG levels negatively correlated and HDL-cholesterol levels positively correlated with the degree of insulin sensitivity (30). No sex difference occurred. Walden et al. (31) in a study of 270 whites with NIDDM showed that the women had a greater increase in fasting TG levels and a greater decrease in HDL-cholesterol levels as compared with the men in the study. Prediabetic Mexican Americans similarly have higher fasting plasma TGs and lower serum HDL cholesterol than nondiabetic cohorts (29).

We chose to stratify our data according to sex because

TABLE 2
Multiple linear regression analysis to determine the influence of insulin sensitivity and obesity as independent variables influencing BP, fasting serum TGs, and serum HDL cholesterol

	Multiple *R*	Partial correlation	
	Glucose Disposal and BMI	Glucose Disposal	BMI
sBP			
Men	0.291 (0.23)	−0.0004 (1.00)	0.266 (0.12)
Women	0.071 (0.90)	−0.049 (0.75)	−0.069 (0.66)
dBP			
Men	0.475 (0.01)	−0.040 (0.82)	0.450 (0.01)
Women	0.165 (0.56)	−0.135 (0.38)	−0.151 (0.33)
Fasting TGs			
Men	0.431 (0.03)	−0.311 (0.07)	0.173 (0.32)
Women	0.394 (0.02)	−0.251 (0.08)	0.157 (0.27)
HDL cholesterol			
Men	0.434 (0.03)	0.350 (0.04)	−0.116 (0.51)
Women	0.251 (0.22)	0.188 (0.20)	0.241 (0.10)

Data are correlation coefficients, with levels of statistical significance in parentheses.

many of the studies showing a positive relationship between insulin resistance and/or hyperinsulinemia are in men, especially white men. The relationship in white women is unclear. Although NIDDM is thought to be part of Syndrome X, the role of insulin resistance in the pathogenesis of hypertension and lipid abnormalities in ethnic groups with a high prevalence rate of NIDDM is uncertain.

Our data do not show a relationship between insulin resistance and BP in either black men or women with NIDDM. Black men with NIDDM do exhibit the changes in lipoproteins seen in NIDDM in other races, especially a decrease in HDL cholesterol with a reciprocal increase in serum TG. Black women with NIDDM, however, do not show this simple reciprocal relationship between serum TG and HDL-cholesterol levels. BMI influences this relationship in women, but has no influence in men. HDL-cholesterol levels in women do not correlate with insulin sensitivity.

Insulin resistance only partially explains the lipid abnormalities in black men with NIDDM, but does not elucidate the abnormalities in black women with NIDDM. The origin of hypertension in the black population with NIDDM is not explained by differences in insulin sensitivity.

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