Insulin Action in Black Americans With NIDDM

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OBJECTIVE — To assess the influences that obesity and hyperglycemia have on insulin action in black NIDDM patients.

RESEARCH DESIGN AND METHODS — Thirty-nine subjects were studied who had normal GHb levels and/or FPG <6.4 mM and who had not taken pharmacological agents for 2–91 mo before the study. Insulin action was studied using the euglycemic insulin clamp with a D-[3-^{3}H]glucose infusion. Degree of obesity was assessed with BMI. During carefully monitored follow-up, 9 patients relapsed into a hyperglycemic state, and insulin action was restudied after acute reregulation of their plasma glucose.

RESULTS — Insulin action was related to the degree of obesity at the extremes of BMI: 7 of 8 patients (87.5%) with a BMI <24.0 kg/m^2 were insulin sensitive, and 8 of 9 patients (88.9%) with a BMI >28.5 kg/m^2 were insulin resistant. In the midrange BMI (24.0–28.5 kg/m^2), patients were equally likely to be insulin resistant or insulin sensitive. A plot of frequency versus glucose disposal in those patients was compatible with a bimodal distribution ($P < 0.025$): 12 of 22 patients were normally insulin sensitive (glucose disposal 6.1–9.4 mg · kg^{-1} · min^{-1}), and 10 were insulin resistant (glucose disposal 2.4–4.8 mg · kg^{-1} · min^{-1}). Analysis of this midrange BMI group showed that in the insulin-sensitive group, an inverse relationship existed between BMI and glucose disposal ($r = -0.64$, $P < 0.05$), whereas no such relationship was found in the insulin-resistant group. The clinical characteristics of the midrange BMI group indicated that fasting plasma insulin, total cholesterol, and triglycerides were higher; whereas BMI, age, and FPG were not different in the insulin-resistant compared with the insulin-sensitive group. With the development of hyperglycemia, insulin action in the insulin-sensitive group was decreased, independent of obesity, whereas it was unchanged in the insulin-resistant group.

CONCLUSIONS — Insulin resistance exists in only ~50% of black NIDDM patients. The relationship between obesity and insulin resistance is not a simple one. The data can be explained by one of two hypotheses: *1)* insulin resistance in black NIDDM patients is an acquired defect related to the development of obesity and is modulated by hyperglycemia, or *2)* NIDDM exists as two variants, one with primary insulin resistance and one with normal insulin sensitivity, and that insulin resistance causes central and/or generalized obesity.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; GHb, GLYCOSYLATED HEMOGLOBIN; FPG, FASTING PLASMA GLUCOSE; BMI, BODY MASS INDEX; ADA, AMERICAN DIABETES ASSOCIATION; CV, COEFFICIENT OF VARIANCE; R_a, RATE OF APPEARANCE; R_d, RATE OF DISAPPEARANCE; OGTT, ORAL GLUCOSE TOLERANCE TEST; ANOVA, ANALYSIS OF VARIANCE; NS, NO SIGNIFICANCE.

The sequence of events responsible for the development of hyperglycemia in NIDDM patients continues to be unresolved. One hypothesis is that the underlying genetic defect is insulin resistance, and hyperglycemia develops later when β-cell insulin secretion cannot be maintained at a high enough level to compensate for the resistance. Studies in Pima Indians with normal, impaired, and diabetic glucose tolerance (1), in nondiabetic offspring of Mexican-American NIDDM patients (2), and in nondiabetic first-degree relatives of Finnish NIDDM patients (3) support the hypothesis of primary insulin resistance. The other hypothesis is that the primary defect is a deficiency of insulin secretion and that insulin resistance occurs secondarily. Studies showing amelioration of insulin resistance in NIDDM patients by normoglycemic regulation (4,5) and those showing defects in insulin secretion in nondiabetic relatives of NIDDM patients (6,7) or very early in the course of NIDDM (8) support a primary defect in insulin secretion as the cause of NIDDM.

The nature of the underlying abnormality in NIDDM has profound implications. If NIDDM is the result of a primary cellular defect in insulin action, then the development of NIDDM should be preceded by a long period of hyperinsulinemia and an increased risk factor profile for macrovascular disease (9).

Hyperglycemia and obesity would be expected to exert minimal effects on this insulin resistance. On the other hand, if NIDDM is caused by a primary deficiency of insulin secretion, and if insulin resistance is secondary to factors such as hyperglycemia and/or obesity, then the time preceding the development of hyperglycemia should be characterized by normal or low plasma insulin levels and a relatively normal risk factor profile for macrovascular disease. Furthermore, reduction in hyperglycemia and obesity should ameliorate the insulin resistance.

We have reported previously that NIDDM patients who were in a near-normoglycemic remission when off pharmacological therapy for 2–91 mo showed two different patterns of metabolic abnormalities (10,11). The data suggested that NIDDM actually may be two distinct disorders—one characterized by a primary defect in insulin action and the other with normal insulin action and presumably a primary β-cell abnormality. The variant with normal insulin action was observed only in black NIDDM patients.

This study focuses on black NIDDM patients and assesses the relationship of obesity and the development of hyperglycemia to insulin action in these patients.

RESEARCH DESIGN AND METHODS

— The study population consisted of 39 black patients who had presented with severe hyperglycemia. Most had required initial hospitalization and treatment with intravenous fluids and insulin. Outpatient treatment consisted of insulin and/or oral hypoglycemic sulfonylureas for 1 wk-45 mo. Pharmacological treatment was discontinued because of hypoglycemic symptoms or demonstration of lack of need. These patients had been near normoglycemic for 2–91 mo and off all pharmacological treatment at the time of this study. A complete description of the clinical characteristics of these patients has been published previously (12). The patients had been on their ordinary ADA diet, and their body weight had been stable for a minimum 3 mo before studies were conducted. No patient had significant renal, hepatic, or cardiac disease, and none were using agents known to affect glucose metabolism.

Near normoglycemia is defined as a GHb level in the normal range (37 of 39 patients) and/or FPG <6.4 mM (33 of 39 patients). FPG in this population was 5.9 ± 0.7 mM (range, 4.6 to 7.2 mM). The degree of obesity was defined in terms of the BMI, determined by weight/square of height (kg/m^2).

The control population for glucose disposal consisted of 9 normal, nondiabetic volunteers (5 black, 3 white) whose mean age was 45 yr (range 31–59 yr), and whose BMI/(mean ± SD) was 25.2 ± 3.0 kg/m^2. All subjects had consumed ≥150 g of carbohydrate for 3 days before the study.

The study was approved by the institutional review board of the State University of New York, Health Science Center at Brooklyn. All patients signed an informed consent and were studied at the Clinical Research Center at University Hospital in Brooklyn.

Insulin secretion

A standard 75 g OGTT was performed with blood samples obtained at 0, 30, 60, 90, and 120 min for plasma glucose and insulin determinations.

Insulin sensitivity

Insulin sensitivity was measured with the euglycemic hyperinsulinemic clamp and a D-[3-^{3}H]glucose infusion (13) as described previously (10). An antecubital vein was cannulated retrograde and kept in a warming box at 68°C to provide arterialized venous blood for sampling. D-[3-^{3}H]Glucose was infused for 150 min before beginning the insulin infusion. Insulin infusion was begun with a priming insulin dose for the initial 10 min in a logarithmically decreasing manner. This manner was used to acutely raise the serum insulin to the desired level where it was maintained for 120 min by a continuous insulin infusion. The serum glucose was measured every 5 min and was maintained at the patient's fasting euglycemic level with a CV of 5%. The overall glucose disposal rate was assessed with plasma D-[3-^{3}H]glucose–specific activity for each of three 20-min intervals during the 2nd h of the insulin infusion when steady-state levels had been achieved. This mean value was used as the data point for the study. Urinary glucose loss was not present because the measurements were made while patients were euglycemic. The patients were studied in the basal state and at insulin infusion rates of 0.25 and 1.0 $mU \cdot kg^{-1} \cdot min^{-1}$ consecutively, each for 120 min. The 0.25 $mU \cdot kg^{-1} \cdot min^{-1}$ insulin dose was used to define the extent of suppression of hepatic glucose production and glucose disposal. The 1.0 $mU \cdot kg^{-1} \cdot min^{-1}$ insulin dose was used to measure overall glucose disposal and define in vivo insulin sensitivity, presumably primarily at the level of muscle. The glucose R_a and overall R_d were measured during the basal and insulin-infused states by infusing D-[3-^{3}H]glucose in a primed continuous manner. A priming dose (236 $nCi \cdot kg^{-1} \cdot min^{-1}$) was given as a bolus, followed by a continuous infusion (2.36 $nCi \cdot kg^{-1} \cdot min^{-1}$).

After a 150-min equilibration period (which resulted in stable plasma glucose-specific activity), blood samples were drawn every 15 min throughout the study for additional glucose-specific activity measurements. Steele's equations for non–steady-state kinetics were used to determine R_a and R_d (14). The glucose disposal is the sum of exogenously administered glucose and hepatic glucose production.

Insulin sensitivity during hyperglycemic relapse was measured in 9 patients. The patients had developed hyperglycemia recently and were untreated. The plasma glucose levels were brought down to their initial euglycemic values by an insulin infusion (1 $mU \cdot kg^{-1} \cdot min^{-1}$) for 30–120 min before the start of the repeat study.

Immunological studies

Islet cell cytoplasmic antibodies were measured by G. Eisenbarth and R. Jackson with Wistar-Furth rat pancreases as a substrate, an anti-islet monoclonal antibody (A2 B5) to identify islets, and fluorescein-conjugated protein A to identify patient autoantibodies (15).

Analytical method

Plasma glucose was measured by a glucose oxidase method with a Beckman glucose analyzer (Fullerton, CA). Plasma insulin was measured with a double-antibody radioimmunoassay technique with a lower limit of detection of 2.5 uU/ml (16). Specific activity of D-[3-^{3}H]glucose was determined on plasma samples deproteinized with barium hydroxide and zinc sulfate.

Materials

Human insulin was supplied by Eli Lilly (Indianapolis, IN). D-[3-^{3}H]Glucose (13.5 Ci/mmol) was purchased from DuPont-NEN (Boston, MA) and had been chromatographed to 98% purity by high-performance liquid chromatography.

Statistical analysis

Multiple group means were compared by ANOVA, and the Student-Neuman Keuls procedure was used to determine paired comparisons at $P = 0.05$ (17). Correlations were determined by linear regression analysis. Bimodality of the distribution of insulin action was tested according to Haldane using the Z distribution (18). Glucose excursion and insulin response to oral glucose was calculated as the area under the curve by trapezoidal estimation. Values are expressed as mean ± SE unless otherwise stated.

RESULTS

Relationship of obesity to insulin action

Glucose uptake in response to a 1 mU · kg^{-1} · min^{-1} insulin infusion in our 39 near-normoglycemic black NIDDM patients ranged from 2.2 to 9.36 mg · kg^{-1} · min^{-1}. We examined our data to determine whether the degree of obesity might be the major determinant of insulin action in this population. The distribution of insulin-mediated glucose disposal versus BMI is shown in Figure 1: 8 of 9 (88.9%) black NIDDM patients with a BMI >28.5 kg/m^2 were insulin resistant, whereas 7 of 8 (87.5%) black NIDDM patients with a BMI <24 kg/m^2 were insulin sensitive. In the midrange of BMI (24.0–28.5 kg/m^2), patients were equally likely to be insulin resistant or insulin sensitive. The data indicate that the degree of obesity appears to correlate with insulin action at the two extremes of BMI, whereas in the midrange of BMI (24–28.5 kg/m^2), such a relationship is not obvious. Plasma insulin levels during the 1 mU · kg^{-1} · min^{-1} insulin clamp were similar in both groups (97 ± 3 and 104 ± 6 uU/ml in the insulin-sensitive and insulin-resistant group, respectively).

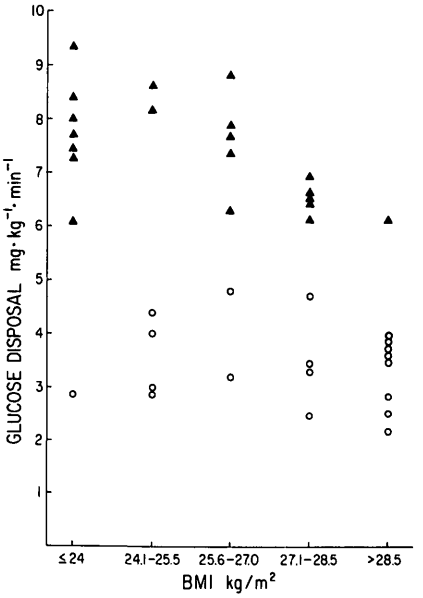

Figure 1. *Distribution of insulin-mediated glucose disposal in relation to BMI during a 1 mU · kg^{-1} · min^{-1} insulin infusion.*

Figure 2 shows that insulin action in response to 1 mU · kg^{-1} · min^{-1} insulin infusion in patients whose BMI was 24.0–28.5 kg/m^2 ($n = 22$) was consistent with a bimodal distribution ($P < 0.025$). Twelve of the 22 patients were normally sensitive to insulin with glucose-disposal values (6.1–9.4 mg · kg^{-1} · min^{-1}) that were not different from normal, nondiabetic control subjects (6.2–8.5 mg · kg^{-1} · min^{-1}).

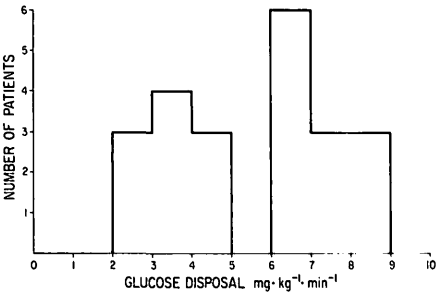

Figure 2. *Frequency distribution of insulin-mediated glucose disposal during a 1 mU · kg^{-1} · min^{-1} insulin infusion in subjects with a BMI of 24.0–28.5 kg/m^2. Distribution is bimodal, $P < 0.025$.*

Ten subjects were insulin resistant with glucose disposals ranging from 2.2 to 4.8 mg · kg^{-1} · min^{-1}. Basal glucose disposal and insulin sensitivity to 0.25 mU · kg^{-1} · min^{-1} insulin infusion also were statistically significantly lower in the insulin-resistant group compared with the insulin-sensitive group (1.64 ± 0.33 and 1.63 ± 0.28 mg · kg^{-1} · min^{-1} vs. 1.95 ± 0.17 and 2.31 ± 0.41 mg · kg^{-1} · min^{-1}, respectively, $P < 0.05$ and $P < 0.001$). The insulin-sensitive group had basal and low-dose, insulin-mediated glucose disposal that was similar to the normal, nondiabetic control subjects (2.1 ± 0.24 and 2.56 ± 0.44 mg · kg^{-1} · min^{-1}).

Table 1 compares the clinical characteristics of the insulin-sensitive ($n = 12$) and insulin-resistant ($n = 10$) subjects with BMI 24.0–28.5 kg/m^2. No significant differences in age, sex distribution, or glycemic control were found. Although no differences in BMI were observed (26.3 ± 0.40 and 26.34 ± 0.40 kg/m^2), fasting plasma insulin was significantly higher in the insulin-resistant group compared with the insulin-sensitive group. The differences in mean insulin-mediated glucose disposal are obvious. Table 1 also compares the clinical characteristics of the lean and midrange BMI insulin-sensitive groups who differed only in BMI, not in age, sex distri-

Table 1—Characteristics of various insulin-sensitive and insulin-resistant subjects as defined by degree of obesity

	N	Age (yr)	Men/ women	BMI (kg/m^2)	Glucose disposal (mg · kg^{-1} · min^{-1})	Fasting plasma insulin (uU/ml)*	FPG (mM)	Triglyceride (mM)	Total cholesterol (mM)†	High-density lipoprotein cholesterol (mM)
Insulin-sensitive subjects										
BMI <24.0 kg/m^2	7	46.6 ± 4.6	5/2	23.3 ± 0.8	7.8 ± 1.0	9.6 ± 3.8	5.89 ± 0.78	0.65 ± 0.15	4.11 ± 0.80	1.09 ± 0.22
BMI 24.0–28.5 kg/m^2	12	48.6 ± 8.0	7/5	26.5 ± 1.1	7.3 ± 0.9	8.2 ± 4.9	5.33 ± 1.44	0.91 ± 0.38	4.39 ± 1.14	1.34 ± 0.34
Insulin-resistant subjects										
BMI 24.0–28.5 kg/m^2	10	45.5 ± 9.5	4/6	26.3 ± 1.5	3.6 ± 0.8	18.9± 5.7§	5.94 ± 0.78	1.63 ± 0.60§	5.53 ± 0.96§	1.11 ± 0.24
BMI >28.5 kg/m^2	8	50.5 ± 8.0	5/3	32.1 ± 3.4	3.2 ± 0.7	14.8 ± 3.8	6.11 ± 0.33	1.52 ± 0.45	6.23 ± 1.03	1.19 ± 0.23

Values are means ± SD.
*ANOVA, $P = 0.001$.
†ANOVA, $P = 0.0017$.
‡ANOVA, $P = 0.0054$.
§$P < 0.05$, insulin-resistant vs. insulin-sensitive subjects with BMI 24.0–28.5 kg/m^2.

bution, fasting plasma insulin, glycemic control, or insulin-mediated glucose disposal. Likewise, the obese and midrange BMI insulin-resistant groups also differed only in BMI. Thus, obesity seems not to be the sole determinant of insulin-mediated glucose disposal or fasting plasma insulin level in black near-normoglycemic NIDDM patients. Similarly, fasting plasma triglyceride and total cholesterol levels were higher in the insulin-resistant subjects compared with insulin-sensitive subjects, suggesting that obesity is not the only determinant of lipid levels. No significant differences were found in high-density lipoprotein cholesterol levels among the groups. Anti-islet cell antibodies (data not shown) were absent in all patients.

Next, we attempted to discern what relationship, if any, existed between glucose disposal and BMI in the weight-matched (BMI, 24.0–28.5 kg/m^2) insulin-sensitive and insulin-resistant groups. Figure 3 shows the significant inverse correlation between insulin action and BMI in the insulin-sensitive patients (closed circles) ($r = -0.64$, $P < 0.05$). In contrast, the insulin-resistant patients showed no such correlation (Fig. 3; open circles) ($r = -0.14$, NS). If the weight-matched subsets are analyzed as a single group, no significant correlation between insulin action and BMI was found ($r = 0.14$, NS).

Effect of hyperglycemia on insulin secretion and action

During the course of long-term follow-up, 9 patients (4 insulin-sensitive and 5 insulin-resistant patients) had a relapse from their near-normoglycemic state into a hyperglycemic state. Table 2 lists the BMI, glucose metabolism, and insulin secretion in those patients. The relapse was not associated with a significant change in body weight as assessed by BMI or any known precipitating event. FPG rose comparably in the 4 insulin-sensitive and 5 insulin-resistant patients (Table 2, Fig. 4). The deterioration in glucose metabolism was not associated with any change in fasting plasma insulin levels but was associated with a ~75% decrease in insulin secretion in response to a 75 g oral glucose load in both insulin-sensitive and insulin-resistant patients (Table 2).

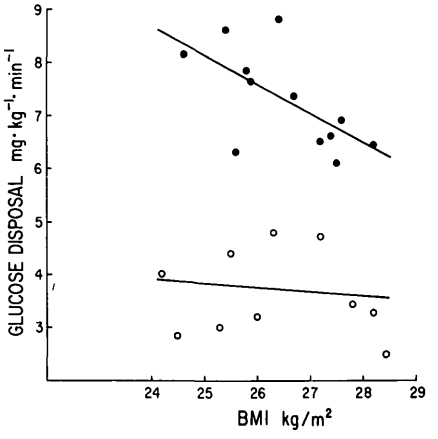

Figure 3. *Insulin-mediated glucose disposal (1 mU · kg^{-1} · min^{-1}) versus BMI (24.0–28.5 kg/m^2). In insulin-sensitive subjects, (●) glucose disposal is related to BMI inversely ($r = -0.64$, $P < 0.05$, $y = -0.55x + 21.86$. In insulin-resistant subjects (○), no such correlation was found. $n = 0.14$, NS.*

In spite of the comparable deterioration of glucose metabolism, a significant decrease in insulin action with the development of hyperglycemia occurred only in the insulin-sensitive patients. Figure 4 shows that euglycemic, hyperinsulinemic clamps (insulin infusion of 1 mU · kg^{-1} · min^{-1}) conducted in the insulin-sensitive patients at the same plasma glucose levels as during their initial studies resulted in a decrease in mean glucose disposal (8.0 ± 0.4 to 5.8 ± 0.3 mg · kg^{-1} · min^{-1}, $P < 0.01$). The glucose disposals, as measured by the euglycemic hyperinsulinemic clamp during relapse in the insulin-resistant group, were unchanged from the initial values (3.6 ± 0.4 vs. 3.6 ± 0.5 mg · kg^{-1} ·

Table 2—Plasma insulin and glucose levels after relapse into the hyperglycemic state

				OGTT (0–120 min^{-1})	
	BMI (kg/m^2)	FPG (mM)	Fasting plasma insulin (uU/ml)	Glucose area (mmol · min · l^{-1})	Incremental insulin area (uU · min · ml^{-1})
Insulin-sensitive subjects (N = 4)					
Remission	24.1 ± 0.9	5.8 ± 0.2	7.0 ± 3.1	1437 ± 107	2845 ± 830
Relapse	24.1 ± 1.2	12.9 ± 1.2*	8.2 ± 1.2	2379 ± 248†	654 ± 325‡
Insulin-resistant subjects (N = 5)					
Remission	29.3 ± 2.4	5.8 ± 0.3	16.9 ± 3.0	1209 ± 63	6191 ± 563§
Relapse	29.7 ± 2.9	12.8 ± 1.3*	18.6 ± 4.1	2110 ± 145†	1612 ± 687‖

Values are means ± SE.
*P < 0.001 compared with the remission state.
†P < 0.02 compared with the remission state.
‡P < 0.05 compared with the remission state.
§P < 0.02 insulin resistant compared with insulin sesnsitive.
‖P < 0.005 compared to the remission state (n = 4, one individual had insulin antibodies).

min^{-1}). Thus, the hyperglycemic state decreased insulin sensitivity in insulin-sensitive patients but had no effect on insulin sensitivity in the insulin-resistant group.

A rise in basal hepatic glucose production also was associated with the development of hyperglycemia in both groups. In the insulin-sensitive group, it rose from 1.9 ± 0.9 to 2.8 ± 0.2 mg · kg^{-1} · min^{-1} (P < 0.01). In the insulin-resistant group, it rose from 1.55 ± 0.15 to 2.47 ± 0.36 mg · kg^{-1} · min^{-1} (P < 0.05).

Reproducibility of insulin sensitivity measurements

A major problem in evaluating differences and changes in insulin sensitivity in normal, nondiabetic control subjects and NIDDM patients is having a valid measure of the variability of replicate measurements taken over time. This is particularly important in our study, because we have attempted to define discrete NIDDM populations and different patterns of regulation of insulin sensitivity.

During the course of long-term follow-up and metabolic studies on our near-normoglycemic black NIDDM insulin-sensitive and insulin-resistant groups, we obtained serial studies on numerous patients who have maintained near normoglycemia and have not gained significant weight. Table 3 lists these data. After intervals of 3 wk-24 mo, the glucose disposal caused by a 1 mU · kg^{-1} · min^{-1} insulin infusion was not changed significantly in either insulin-sensitive or insulin-resistant NIDDM patients. These data establish the stability of this measurement by the technique we have used.

CONCLUSIONS— When insulin action was measured in 39 black NIDDM patients without confounding influences of chronic hyperglycemia or pharmacological therapy, <50% were insulin resistant. NIDDM among black individuals, therefore, consists of two distinct metabolic profiles: one with insulin resistance and one with normal insulin action and primary insulin deficiency. The insulin-sensitive group is not an IDDM group because the clinical course of the patients in that group was that of NIDDM—they secreted significant, albeit not sufficient, quantities of insulin, and they did not have anti-islet cell antibodies in their serum. They also had an HLA DR3 and DR4 frequency that was comparable with a normal, nondiabetic black population.

The role of obesity in determining insulin action in this group is complex. Eight of 9 patients with a BMI >28.5 kg/m^2 were insulin resistant, whereas 7 of 8 patients with a BMI <24 kg/m^2 were insulin sensitive. Thus, it might seem reasonable to conclude that black NIDDM patients are normally sensitive to insulin, and that insulin resistance can be explained primarily by the development of obesity. This relationship, however, breaks down in the large group with a BMI of 24.0–28.5 kg/m^2. These patients are equally likely to be insulin sensitive or insulin resistant throughout the BMI range (Fig. 1). If one assumes that they represent a single population, no correlation between BMI and insulin-mediated glucose disposal exists (r = 0.14). This might be explained by a correlation between insulin-mediated glucose disposal and intra-abdominal fat content rather than BMI. Unfortunately, adequate quantitative measurements of intra-abdominal fat have not been conducted as yet.

If, however, one assumes (as shown in Fig. 2) that this population

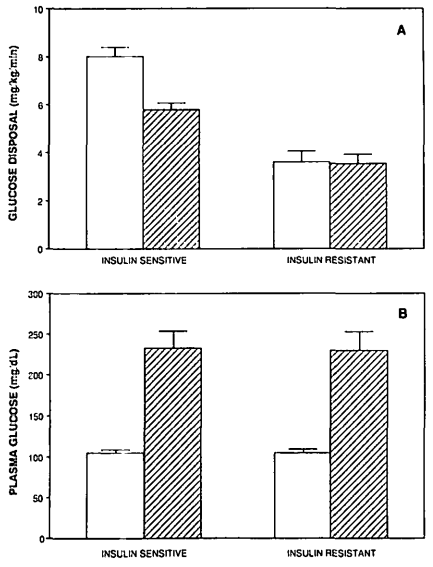

Figure 4. *Glucose disposal and plasma glucose levels (▨, hyperglycemic state; □, near-normoglycemic state). A, insulin-mediated (1 mU · kg^{-1} · min^{-1}) glucose disposal (mg · kg^{-1} · min^{-1}) before and after development of hyperglycemia in 4 insulin-sensitive and 5 insulin-resistant patients. Glucose disposal decreased significantly in the insulin-sensitive group (from 8.0 ± 0.4 to 5.8 ± 0.3 mg · kg^{-1} · min^{-1}) with the development of hyperglycemia (P < 0.01). No significant change was seen in glucose disposal in the insulin-resistant group (3.6 ± 0.5 to 3.6 ± 0.4 mg · kg^{-1} · min^{-1}) with the development of hyperglycemia. B, plasma glucose before and after the development of hyperglycemia was not different in the insulin-sensitive (5.8 ± 0.2 to 12.4 ± 1.2 mM [104 ± 4 to 224 ± 22 mg/dl]) and insulin-resistant (5.8 ± 0.3 to 12.8 ± 1.3 mM [104 ± 5 to 230 ± 24 mg/dl]) groups. Values are means ± SE.*

actually represents two discrete populations, then the insulin-sensitive group shows a significant inverse correlation between insulin-mediated glucose disposal and BMI, whereas the insulin-resistant one shows no correlation (Fig. 3). Our data, therefore, indicate a high degree of correlation between the degree of obesity and insulin resistance at the extremes of BMI and a variable relationship in the midrange.

Table 3—Reproducibility of insulin-mediated glucose disposal in NIDDM patients under conditions of near-normoglycemia and stable body weight

Patient no.	Interval between baseline and subsequent studies (mo)	FPG (mM)	BMI (kg/m^2)	Insulin (1 mU · kg^{-1} · min^{-1})-mediated glucose disposal (mg · kg^{-1} · min^{-1})
4	—	5.2	23.4	7.7
	4	6.1	23.5	6.8
5	—	6.6	26.7	8.7
	0.75	5.8	26.3	8.9
7	—	7.1	26.5	7.6
	8	6.4	26.5	7.7
6	—	6.8	30.5	6.3
	10	6.6	30.2	5.9
	24	6.5	30.5	6.1
12	—	6.2	28.8	2.7
	6	6.2	29.0	3.0
13	—	4.8	28.4	2.5
	9	4.4	29.0	3.0
15	—	5.2	33.2	3.2
	8	5.6	33.4	3.2
	16	5.1	33.8	3.1

Basal hepatic glucose production was lower in the insulin-resistant group compared with the insulin-sensitive group. This is consistent with the higher basal plasma insulin values seen in the insulin-resistant group, and implies that the liver responds normally to the suppressive effects of insulin in spite of insulin resistance in peripheral tissues (10).

Our data in black NIDDM patients vary somewhat from published data in other NIDDM populations. Normal weight individuals with either impaired glucose tolerance or NIDDM have been reported to have significantly impaired insulin-mediated glucose disposal (1,3). This impaired insulin-mediated glucose disposal of NIDDM patients has been shown repeatedly to be independent of BMI over the range 24–38 kg/m^2 (19–26).

Recently, Arner et al. (27) reported data somewhat similar to our own in elderly, newly diagnosed diabetic men. Although they identify both insulin-resistant and insulin-sensitive patients, the difference is attributed to obesity: nonobese diabetics showed normal peripheral insulin sensitivity with only an insulin secretory defect, whereas obese diabetic patients showed peripheral insulin resistance in combination with an insulin secretory defect.

The inverse correlation between BMI and insulin-mediated glucose disposal in the BMI range 24.0–28.5 kg/m^2 that we found in our insulin-sensitive patients is similar to that noted in nondiabetic whites and Pima Indians by Bogardus et al. (28). Those researchers found an inverse relationship between body fat (range 10–30%) and insulin-mediated glucose disposal. Yki-Jarvinen and Koivisto (29) noted the same inverse relationship between body fat (range 2–14%) and insulin-mediated glucose disposal in 23 normal-weight, healthy, nondiabetic males. Campbell and Gerich (30) have presented data in nondiabetic obese individuals showing that obesity adversely affects insulin-mediated glucose disposal only beyond a BMI of 26.8 kg/m^2. The reasons for the differences in their data from that of Bogardus and Yki-Jarvinen are unclear.

Hyperglycemia affected insulin action differently in the insulin-sensitive group compared with the insulin-resistant group. As shown in Table 2, hyperglycemic relapse was associated with a marked reduction in glucose-mediated insulin secretion in the insulin-sensitive group. Insulin action, which was normal initially, decreased by 27.5% with the development of hyperglycemia (Fig. 4). This indicated that insulin action is modulated by glycemia in the insulin-sensitive NIDDM group, as reported in some NIDDM subjects and in normal, nondiabetic animal models (4,5,31,32). In contrast, the development of hyperglycemia in the insulin-resistant group had no effect on the already impaired insulin action. Insulin action in the insulin-resistant group is, therefore, independent of glycemic regulation. Relapse from normoglycemia to hyperglycemia in the insulin-sensitive group was caused by decreased insulin secretion and a concomitant decrease in insulin action. Development of hyperglycemia in the insulin-resistant group was caused only by a decrease in insulin secretion. Thus, a critical loss of insulin secretion appears to be essential to the development of hyperglycemia.

The data presented in this report are compatible with any of several hypotheses concerning the pathogenesis of NIDDM. One that appeals to us is that NIDDM in black individuals is actually two separate and discrete disorders. One disorder is characterized by a primary genetic abnormality in insulin action that results in insulin resistance. This insulin resistance is severe and is affected only minimally by obesity or hyperglycemia. Hyperglycemia develops when insulin secretion can no longer compensate for insulin resistance. Insulin resistance contributes to the development of obesity. Cardiovascular disease risk factors are likely increased as a result of the insulin-resistance syndrome (11). The other disorder is characterized by a primary deficiency of β-cell function. Insulin resistance occurs only as a consequence of obesity and/or hyperglycemia. Cardiovascular risk factors probably would not be increased unless secondary insulin resistance occurred.

Another hypothesis is that black NIDDM patients are insulin-sensitive. Insulin resistance would occur only in those who develop central obesity. Hyperglycemia would cause insulin resistance independently. Cardiovascular disease risk factors would increase only after the secondary insulin resistance had developed. Our recent observations that specific enrichment of the frequency of different HLA-DQ subtypes characterize insulin-sensitive and insulin-resistant NIDDM in black individuals would favor the two disorder hypothesis (33).

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References

1. Lillioja S, Mott DM, Howard BV, Bennett PH, Yki-Jarvinen H, Freymond D, Nyomba BL, Zurlo F, Swinburn B, Bogardus C: Impaired glucose tolerance as a disorder of insulin action: longitudinal and cross-sectional studies in Pima Indians. *N Engl J Med* 318:1217–25, 1988
2. Haffner SM, Stern MP, Hazuda HP, Pugh JA, Patterson JK: Hyper-insulinemia in a population at high risk for non-insulin-dependent diabetes mellitus. *N Engl J Med* 315:220–24, 1986
3. Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widen E, Schalin C, Groop L: Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med* 321:337–43, 1989
4. Scarlett JA, Gray RS, Griffin J, Olefsky JM, Kolterman OG: Insulin treatment reverses the insulin resistance of type II diabetes mellitus. *Diabetes Care* 5:353–63, 1982
5. Simonson DC, Ferrannini E, Bevilacqua S, Smith D, Barrett E, Carlson R, DeFronzo RA: Mechanism of improvement in glucose metabolism after chronic glyburide therapy. *Diabetes* 33:838–45, 1984
6. O'Rahilly SP, Turner RC, Matthews DR: Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. *N Engl J Med* 318: 1225–30, 1988
7. O'Rahilly SP, Nugent Z, Rudenski AS, Hosker JP, Burnett MA, Darling P, Turner RC: β-cell dysfunction, rather than insulin insensitivity is the primary defect in familial type 2 diabetes. *Lancet* 2:360–64, 1986
8. Temple RC, Carrington CA, Luzio SD, Owens DR, Schneider AE, Sobey WJ, Hales CN: Insulin deficiency in non-insulin-dependent diabetes. *Lancet* 1:293–95, 1989
9. Reaven GM: The role of insulin resistance in human disease. *Diabetes* 37: 1595–1607, 1988
10. Banerji MA, Lebovitz HE: Insulin-sensitive and insulin resistant variants in NIDDM. *Diabetes* 38:784–92, 1989
11. Banerji MA, Lebovitz HE: Coronary heart disease risk factor profiles in black patients with non-insulin-dependent diabetes mellitus. *Am J Med* 91:51–58, 1991
12. Banerji MA, Lebovitz HE: Remission in non-insulin-dependent diabetes mellitus: clinical characteristics of remission and relapse in black patients. *Medicine* 69:176–85, 1990
13. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–23, 1979
14. Steele R: Influences of glucose loading and of injected insulin on hepatic glucose output. *Ann NY Acad Sci* 82:420–30, 1959

15. Dib SA, Coleman PG, Dotta F, Tautkus M, Rabizadeh A, Eisenbarth GS: Expression of cytoplasmic islet cell antigens by rat pancreas. *Diabetes* 36:982–85, 1987
16. Morgan CR, Lazarow A: Immunoassay of insulin: two antibody system: plasma insulin levels of normal, subdiabetic and diabetic rats. *Diabetes* 12:115–26, 1963
17. Snedecor GW, Cochran WG: *Statistical Methods.* Iowa State Univ. Press, Ames, 1980, p. 235
18. Haldane JBS: Simple tests for bimodality and bitangentiality. *Ann Eugenics.* 16: 359–64, 1951–1952
19. Ginsberg H, Kimmerling G, Olefsky JM, Reaven GM: Demonstration of insulin resistance in untreated adult onset diabetic subjects with fasting hyperglycemia. *J Clin Invest* 155:454–61, 1975
20. Kolterman OG, Gray RS, Griffin J, Burstein P, Insel J, Scarlett JA, Olefsky JM: Receptor and post-receptor defects contribute to the insulin resistance in non-insulin-dependent diabetes mellitus. *J Clin Invest* 68:957–69, 1981
21. DeFronzo RA, Gunnarsson R, Bjorkman O, Olsson M, Wahren J: Effects of insulin on peripheral and splanchnic glucose metabolism in non-insulin dependent (Type I) diabetes mellitus. *J Clin Invest* 76:149–55, 1985
22. DeFronzo RA, Simonson D, Ferrannini E: Hepatic and peripheral insulin resistance: a common feature of type II (non-insulin-dependent) and type I (insulin-dependent) diabetes mellitus. *Diabetologia* 23:313–19, 1982
23. Reaven GM, Hollenbeck CB, Chen Y-DI: Relationship between glucose tolerance, insulin secretion and insulin action in non-obese individuals with varying degrees of glucose tolerance. *Diabetologia* 32:52–55, 1989
24. DeFronzo RA: The triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 37:667–87, 1988
25. Hollenbeck CB, Chen Y-DI, Reaven GM: A comparison of the relative effects of obesity and non-insulin-dependent diabetes mellitus on in vivo insulin-stimulated glucose utilization. *Diabetes* 33: 622–26, 1984
26. Firth R, Bell P, Rizza R: Insulin action in non-insulin-dependent diabetes mellitus: the relationship between hepatic and extra-hepatic insulin resistance and obesity. *Metabolism* 36:1091–95, 1987
27. Arner P, Pollare T, Lithell H: Different aetiologies of Type 2 (non-insulin-dependent) diabetes mellitus in obese and non obese subjects. *Diabetologia* 34: 483–87, 1991
28. Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven GM: Relationship between degree of obesity and in vivo insulin action in man. *Am J Physiol* 248: E286–91, 1985
29. Yki-Jarvinen H, Koivisto VA: Effects of body composition on insulin sensitivity. *Diabetes* 32:965–69, 1983
30. Campbell PJ, Gerich JE: Impact of obesity on insulin action in volunteers with normal glucose tolerance: demonstration of a threshold for the adverse effect of obesity. *J Clinic Endocrinol Metab* 70: 1114–18, 1990
31. Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA: Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. *J Clin Invest* 79:1510–15, 1987
32. Sasson S, Cerasi E: Substrate regulation of the glucose transport system in rat skeletal muscle. *J Biol Chem* 261:16827–33, 1986
33. Banerji MA, Norin AJ, Chaiken RC, Lebovitz HE: HLA DQ associations distinguish insulin-resistant and insulin-sensitive variants of NIDDM in Black Americans. *Diabetes Care.* In press