Ethnic Differences in the Glycemic Response to Exogenous Insulin Treatment in the Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM)

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OBJECTIVE — The Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus was conducted in NIDDM patients to determine if a significant difference in HbA_{1c} could be achieved between groups receiving standard and intensive treatment. We observed differences in the response to exogenous insulin between African-Americans and other intensively treated patients. Therefore, we assessed the variations of response and correlated factors that might explain such differences.

RESEARCH DESIGN AND METHODS — One hundred fifty-three men aged 40–69 years with NIDDM for ≤15 years were randomized to either the standard therapy (n = 78) or the intensive therapy (n = 75) arm. Of the 75 patients in the intensive therapy group, 57 completed the study on insulin therapy alone. Of these, 18 were African-Americans and 39 were non–African-Americans. We conducted an analysis of the data collected to determine differences in baseline characteristics, glycemic response, insulin requirement, body weight, exercise, and basal C-peptide level, factors that may explain a difference in response to insulin therapy.

RESULTS — Glycemic control improved in all patients with intensive insulin therapy. African-Americans achieved a greater improvement in HbA_{1c} compared with non–African-Americans with a similar increment in insulin. This difference could not be explained by differences in body weight, activity, concomitant use of other medicines, or insulin-secretory capacity of the pancreas.

CONCLUSIONS — We conclude that ethnic differences may exist in the response to insulin therapy. A knowledge of such differences may aid in achieving good glycemic control, especially since minorities have a greater prevalence of and burden from the microvascular complications of diabetes.

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Abbreviations: DCCT, Diabetes Control and Complications Trial; FSG, fasting serum glucose; $\Delta HbA_{1c}/\Delta$insulin, improvement in HbA_{1c} per unit change in insulin dose; INT, intensive therapy; STD, standard therapy; VA CSDM, Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus.

Diabetes affects some 14 million people in the U.S. (>8 million diagnosed; total prevalence, 6.6% of the U.S. population) and is the fourth leading cause of death by disease; it accounts for an annual total health care cost of more than $90 billion. NIDDM accounts for 85–90% of all cases of diabetes. The prevalence of diabetes in minority populations, including African-Americans, Hispanics, Native Americans, Asian-Americans, and Pacific Islander Americans, is two to six times greater than that in white Americans, and NIDDM is now a significant problem in third-world countries as well. Nearly 8.5% of African-American men and 12.1% of African-American women have diabetes compared with 2.5–8.4% of white Americans (1–4).

African-Americans suffer a significantly greater burden from the complications of diabetes, e.g., retinopathy, nephropathy, limb amputations, and diabetes-related mortality (1–3). Identification of differences in the risk factors and pathogenesis of NIDDM in minority populations is necessary so that primary prevention and secondary intervention measures can be targeted toward these groups.

The Diabetes Control and Complications Trial (DCCT) unequivocally demonstrated a 40–60% reduction in indicators of microvascular complications in patients with IDDM with intense glycemic control (5). It is not certain if the results of the DCCT apply to the much larger population of people with NIDDM (6,7). Some researchers consider it reasonable to offer tight control to otherwise healthy people with NIDDM in the likelihood that a similar underlying mechanism applies to the complications of IDDM and NIDDM (8,9). The Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM) recently completed its feasibility trial to determine if a clinically and statistically significant difference of at least 1.5% in HbA_{1c} could be

achieved and maintained between a group of NIDDM patients on standard therapy (STD) and a group on intensive therapy (INT). During a mean follow-up period of 24 months, a separation of HbA_{1c} of 2% was achieved and sustained (10–12).

Of the 153 patients studied in the VA CSDM, 48 (31.4%) were African-Americans. We sought to determine any differences in glycemic control resulting from intensification of insulin therapy between the African-American and the non–African-American patients, to ascertain any difference in the amount of exogenous insulin required to achieve a similar degree of glycemic control, and to assess factors that might explain a difference in response to intensive insulin treatment.

RESEARCH DESIGN AND METHODS

— One hundred fifty-three adult men aged 40–69 years with NIDDM who were being treated with insulin or a maximum dose of sulfonylurea, whose HbA_{1c} was >3 SDs above normal mean (>6.55%), who had NIDDM for ≤15 years, and who did not have conditions that would preclude intensive treatment or end point evaluation, i.e., they met the inclusion and exclusion criteria described previously (10,11), were randomized to STD or INT. One of the exclusion criteria was hemoglobinopathy or any hematologic condition that interfered with HbA_{1c} measurements (10). Patients in the STD group were treated with one or two injections of insulin per day to avoid excessive hyperglycemia or glycosuria, ketonuria, or hypoglycemia, and outpatient visits were made every 3 months. Patients in the INT group were treated with a stepped regimen of bedtime intermediate- or long-acting insulin (phase 1), continued bedtime insulin with daytime glipizide (phase 2), two injections of insulin per day and discontinuation of glipizide (phase 3), or multiple injections of insulin each day (phase 4) with a goal of normal fasting serum glucose (FSG) of 80–115 mg/dl (4.44–6.38 mmol/l) and HbA_{1c} within 2 SDs of the mean for nondiabetic subjects (4.0–6.1%). Patients had weekly telephone contact, monthly visits, and a comprehensive visit every 3 months. All patients in both groups received similar dietary instructions and treatment for hypertension, dyslipidemia, smoking, and obesity. Baseline characteristics of the patients randomized to INT are summarized in Table 1. Of the 75 patients in the INT group, 26 (34.7%) were African-Americans and the other 49 (65.3%) were non–African-Americans. Eight African-Americans and 10 non–African-Americans who completed the trial while in phase 2 (combination insulin and glipizide) were excluded from this analysis because the measured variables may have been affected by the concomitant use of glipizide. Therefore, 18 African-Americans and 39 non–African-Americans who completed the study in phase 1, 3, or 4 were included in this analysis. Patients in the STD group were not included in this analysis, since it was aimed at evaluating possible ethnic differences in response to intensive insulin therapy. FSG and HbA_{1c} were measured at each visit, and blood chemistry profiles and intercurrent medical events were assessed at each quarterly visit. Fasting C-peptide level was measured at entry and at 2 years. Quality control reports were reviewed by an independent data-monitoring board. Of the specimens, 10% was divided into two samples per specimen and the samples were sent to laboratories that were blinded to the aims of the study. The Pearson correlation coefficient was >0.90 for all assessments. More than 90% of the pairs deviated <10% from the mean (11). Home blood glucose monitoring results and hypoglycemic events were recorded at each visit. A questionnaire was administered by the study coordinator at each site to assess differences in exercise patterns; the activities assessed were number of flights of stairs climbed per day, number of blocks walked per day, sports (hours/week), vigorous activity (hours/day), moderate activity (hours/day), and light activity (hours/day) (10,11).

Table 1—*Baseline characteristics of patients*

	African-Americans	Non–African-Americans	*P* value
n (total in the INT group)	26	49	
n (patients completing study in phases 1, 3, or 4)	18	39	0.24*
Phase 1	4	5	
Phase 3	9	14	
Phase 4	5	20	
Age (years)	60.2 ± 1.6	61.0 ± 1.0	0.69†
Duration of diabetes (years)	8.6 ± 3.0	7.7 ± 3.9	0.39†
BMI (kg/m²)	30.5 ± 0.8	30.5 ± 0.8	1.0†
Previous treatment			0.20*
Insulin only	9 (50.0)	18 (46.2)	
Oral agent only	9 (50.0)	15 (38.5)	
Combination	0 (0.0)	6 (15.3)	
Smoking status			0.31*
Cigarettes	2 (11.1)	8 (20.5)	
Cigars/pipe	2 (11.1)	1 (2.6)	
None	14 (77.8)	30 (76.9)	

Data are *n*, means ± SE, or *n* (%). *P value is from χ^2 test. †P value is from unpaired *t* test.

Statistical analysis

The paired *t* test was used to make comparisons within African-American and non–African-American groups over the different time periods. The unpaired *t* test or Wilcoxon's rank-sum test was used to compare the African-American and non–African-American groups at baseline and at the end of the study and to compare changes between groups in measured variables over time. The χ^2 test was used to compare proportions between the African-American and non–African-American groups. Two-sided tests were performed. A *P* value of 0.05 was considered statistically significant. All results are expressed as means ± SE.

RESULTS

— Table 2 summarizes the effect of treatment on glycemic control in all 75 patients in the INT group (African-Americans, *n* = 26; non–African-Americans, *n* = 49). The initial FSG was almost identical in African-Americans and non–African-Americans (*P* = 0.82), and at the end of the study, both groups had significant reductions in FSG (*P* = 0.0001 from baseline for both groups and *P* = 0.77 between groups). The decrement in FSG was similar in the two groups (*P* = 0.74). Baseline HbA_{1c} was higher in African-Americans than in non–African-Americans (*P* = 0.01), and at the end of the study, both groups had significant reductions in HbA_{1c} (*P* = 0.0001

Table 2—*Effect of treatment in the INT group*

	Baseline value			End of study (final) value			*P* value between baseline and final values	
	AA	Non-AA	P value	AA	Non-AA	P value	AA	Non-AA
Entire INT group (AA, *n* = 26; non-AA, *n* = 49)								
FSG (mmol/l)	11.5 ± 0.7	11.4 ± 0.4	0.82	6.7 ± 0.4	6.8 ± 0.3	0.77	0.0001	0.0001
HbA_{1c} (%)	10.0 ± 0.4	8.9 ± 0.2	0.01	6.9 ± 0.2	7.2 ± 0.1	0.31	0.0001	0.0001
Decrement in FSG (mmol/l)				−4.8 ± 0.8	−4.6 ± 0.6	0.74		
Decrement in HbA_{1c} (%)				−3.1 ± 0.5	−1.7 ± 0.2	0.009		
INT group patients completing in phases 1, 3, or 4 (AA, *n* = 18; non-AA, *n* = 39)								
FSG (mmol/l)	11.8 ± 0.8	11.4 ± 0.6	0.68	6.8 ± 0.5	6.8 ± 0.3	0.95	0.0003	0.0001
HbA_{1c} (%)	10.4 ± 0.5	9.0 ± 0.2	0.002	7.1 ± 0.3	7.2 ± 0.2	0.78	0.0001	0.0001
Decrement in FSG (mmol/l)				−5.0 ± 1.1	−4.6 ± 0.6	0.75		
Decrement in HbA_{1c}				−3.3 ± 0.6	−1.8 ± 0.2	0.01*		
Insulin dose (U)	21.4 ± 2	22.9 ± 2.5	0.7	87.4 ± 9.9	124.9 ± 13.6	0.08	0.0001	0.0001
$\Delta HbA_{1c}/\Delta$insulin				0.047 ± 0.02	0.0095 ± 0.01	0.0003*		
Fasting C-peptide (pmol/ml)	0.52 ± 0.07	0.67 ± 0.06	0.15	0.34 ± 0.05	0.50 ± 0.06	0.1	0.002	0.012
BMI (kg/m²)	30.5 ± 0.8	30.5 ± 0.8	1.0	33.8 ± 1.0	32.3 ± 0.9	0.33	0.0001	0.0001
Increment in BMI (kg/m²)				3.3 ± 0.7	1.8 ± 0.4	0.054		

Data are means ± SE. For baseline and end of study values, *P* values are from unpaired *t* tests; for comparison between baseline and final values, *P* values are from paired *t* tests. *P values are from Wilcoxon's rank-sum test. AA, African-Americans; non-AA, non–African-Americans.

from baseline). The decrement in HbA_{1c} was significantly greater in the African-Americans than in the non–African-Americans ($P = 0.009$).

Among the 18 African-Americans and 39 non–African-Americans who completed the study in phases 1, 3, or 4 (i.e., phases in which insulin alone was used), the FSG decreased to near-normal levels in both groups ($P = 0.0003$ in African-Americans and $P = 0.0001$ in non–African-Americans from baseline; $P = 0.68$ at baseline and $P = 0.95$ at the end of the study between groups) (Table 2). The decrement in FSG was similar in African-Americans and non–African-Americans ($P = 0.75$). Baseline HbA_{1c} was higher in African-Americans than in non–African-Americans ($P = 0.002$), and after treatment, HbA_{1c} decreased in both groups ($P = 0.0001$ from baseline) (Table 2). The decrement was significantly greater in African-Americans than in non–African-Americans ($P = 0.01$) (Fig. 1). Of the 18 African-Americans, 11 (61.1%) achieved a final HbA_{1c} of ≤6.8%, i.e., within 3.5 SDs above the normal mean ($5.05 + 3.5 \times 0.5 = 6.8$), whereas only 14 of the 39 non–African-Americans (35.9%) achieved a final HbA_{1c} of ≤6.8% ($P = 0.07$).

The baseline insulin dose was similar in both groups ($P = 0.7$), but at completion of the study, the African-Americans required less insulin to achieve a similar degree of glycemic control, a difference that missed statistical significance by a small amount ($P = 0.08$) (Table 2). The improvement in HbA_{1c} per unit change in insulin dose ($\Delta HbA_{1c}/\Delta$insulin) was markedly greater in African-Americans when the nonparametric Wilcoxon's rank-sum test was applied ($P = 0.0003$) (Fig. 2).

The duration of NIDDM before the study, smoking status, body weight, and BMI (measured in weight in kilograms divided by height in meters squared) were comparable in African-Americans and non–African-Americans at the beginning of the study (Table 2). At 24 months, patients in both groups had gained weight, by 3.3 kg/m² in African-Americans and 1.8 kg/m² in non–African-Americans ($P = 0.0001$ from baseline for both groups; $P = 0.33$ between the two groups at the end of the study; and $P = 0.05$ for difference in weight change)

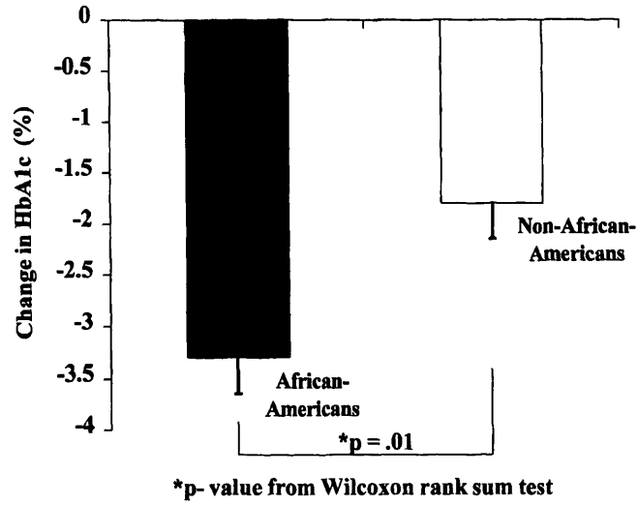

Figure 1—*ΔHbA_{1c} from baseline to final measurement for patients completing the study in phases 1, 3, or 4.*

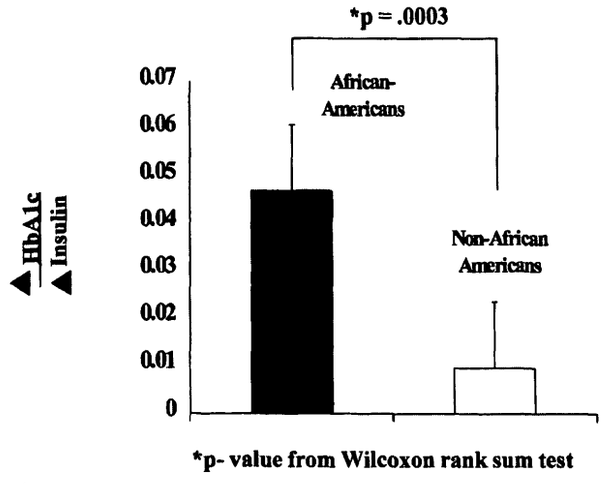

Figure 2—*$\Delta HbA_{1c}/\Delta$insulin for patients completing the study in phases 1, 3, or 4.*

(Table 2). There was no difference in exercise patterns between African-Americans and non–African-Americans at baseline. By the end of the study, African-Americans were doing more light activity than non–African-Americans (13.0 vs. 10.2 h/day; $P = 0.004$). Non–African-Americans were doing more moderate activity than African-Americans (2.1 vs. 0.9 h/day; $P = 0.0008$). The other activity parameters showed no significant differences.

Of all African-Americans, 55.6% were using ACE inhibitors compared with 41.0% of all non–African-Americans ($P = 0.3$). Of all African-Americans, 44.4% were using diuretics compared with 28.2% of all non–African-Americans ($P = 0.2$). The concomitant use of other medicines such as β-receptor agonists/antagonists, α-agonists/antagonists, nicotinic acid, glucocorticoids, anticonvulsants, alcohol, and aspirin, etc., was too infrequent to make a meaningful assessment of its effects.

The fasting plasma C-peptide level, which was not significantly different between the two groups at baseline ($P = 0.15$), decreased in both groups as expected after exogenous insulin administration ($P = 0.002$ in African-Americans and $P = 0.01$ in non–African-Americans from baseline), but the differences between the two groups remained insignificant (Table 2).

CONCLUSIONS — NIDDM is a heterogenous disorder involving both impairment of insulin secretion and resistance to the action of insulin. Pathophysiological differences may exist between and within ethnic groups. Pharmacological therapies, therefore, may have different effects in defined subpopulations of diabetic patients.

Results from the group of patients treated with intensive insulin therapy in the VA CSDM demonstrate that African-American patients were in poorer metabolic control at the beginning of the study than their non–African-American counterparts. Previous studies have shown the existence of race-related differences in the control of diabetes in adults (13). In comparing glycemic control with intensification of insulin therapy and ascertaining differences in the amount of insulin required to achieve such control, we found that both African-Americans and non–African-Americans had highly significant decrements in FSG and HbA_{1c} during a 24-month follow-up period, but the degree of decline in HbA_{1c} was much greater in African-Americans than in non–African-Americans. Similar results were also seen in the entire INT group when patients from all four phases were included. The African-Americans required no more insulin to achieve this decrement than their non–African-American counterparts; in fact, the average final insulin doses were less and the $\Delta HbA_{1c}/\Delta$insulin values were greater in African-Americans than in non–African-Americans. Hence, for a given increment in insulin dose, African-Americans achieved a greater improvement in glycemic control. Several factors could explain this difference in response to insulin intensification.

NIDDM is characterized by progressive hyperglycemia and decreasing β-cell function, regardless of the therapy used, although insulin sensitivity does not deteriorate with time (14,15). Hence, a shorter duration of NIDDM with the presence of relatively intact β-cell function may be associated with better metabolic control and the need for less exogenous insulin in one group. The duration of NIDDM at baseline was similar in African-Americans and non–African-Americans in this study and cannot explain the differences in glycemic control during insulin treatment.

Smoking is associated with insulin resistance and hyperinsulinemia, and smokers tend to have higher waist-to-hip ratios (16). Smoking cessation is associated with weight gain (17). However, the prevalence of smoking was found to be equal in the two groups in this study at baseline and remained unchanged during the study.

One obvious possible explanation for our findings is that during the course of the study, African-Americans weighed less or lost more weight. The prevalence of obesity is higher in African-Americans than in non–African-Americans (18–20). Obesity is accompanied by increased peripheral insulin resistance (21). Loss of weight is associated with improvement in glycemic control (22). Patients in both of our study groups were obese and had identical BMIs at baseline, and patients in both groups gained weight similarly during the study. Hence, the difference in insulin response cannot be explained by changes in body weight between the two groups.

Regular exercise decreases insulin resistance and improves glycemic control (23,24). Patients in both ethnic groups in our study had similar overall activity, and it does not appear that the African-Americans were more sensitive to insulin because they exercised more. Many medicines are known to affect metabolic control in diabetes (25). Although most of these (e.g., diuretics, β-receptor antagonists/agonists, glucocorticoids, anticonvulsants, aspirin, alcohol, etc.) worsen glycemic control, some medicines (e.g., ACE inhibitors and α-adrenergic antagonists) can improve glycemic control. No significant differences, however, were found in the number of patients receiving such medicines.

Another possible explanation for the apparently enhanced glycemic response in African-Americans is the presence of more endogenous insulin. The emergence of NIDDM is associated with an impairment of pancreatic β-cell function and of insulin sensitivity to varying degrees (26). Fasting plasma C-peptide level was used to evaluate

residual insulin-secretory reserve. C-peptide is co-secreted with insulin in an equimolar proportion and is not extracted or metabolized by the liver (27). Similar or lower C-peptide levels but higher plasma insulin concentrations have been found in African-Americans and Afro-Caribbeans in studies examining ethnic differences in plasma C-peptide and insulin levels in relation to glucose tolerance (28–31). Both African-Americans and non–African-Americans had similar levels of C-peptide at baseline in the VA CSDM, and these levels were suppressed equally in both groups with increasing exogenous insulin. The presence of greater endogenous secretory ability does not explain the apparent enhanced glycemic response of African-Americans to insulin.

Differences in duration of diabetes, smoking habits, body weight, activity, concomitant use of other medicines, and fasting C-peptide level, either at baseline or after reduction of hyperglycemia, do not explain the difference in glycemic response to exogenous insulin. It may be that African-Americans in our study either exhibited less hepatic degradation of insulin or were more sensitive to the effects of exogenous insulin. Previous studies have suggested greater impairment in β-cell function, lower hepatic extraction and clearance of insulin, reduced insulin-mediated glucose disposal (insulin sensitivity), and increased glucose-dependent glucose disposal (glucose effectiveness) in African-Americans (28–30). In NIDDM, the degree of fasting and postprandial hyperglycemia is correlated with the basal rate of hepatic glucose production (32). It is possible that intensive insulin therapy in African-Americans was associated with lower hepatic insulin extraction but not its action, thereby suppressing hepatic glucose production and enhancing peripheral glucose uptake, thus achieving better glycemic control compared with that found in non–African-Americans for a given increment in insulin dose.

Another possible explanation for the enhanced insulin effect in the African-American group is the higher initial HbA_{1c} level in this group. Ethnic group and initial HbA_{1c} are confounding factors, and their differential effects could not be distinguished in this study.

Finally, in a study of African-Americans with previous histories of NIDDM who were in remission, NIDDM was found to consist of insulin-resistant (56%) and insulin-sensitive (44%) variants (33). The degree of obesity appeared to correlate with insulin resistance in the lean and clearly obese patients. In the insulin-sensitive group, insulin action was modulated by glycemia, and recurrence of hyperglycemia in the previously normoglycemic patients was associated with a marked reduction in glucose-mediated insulin secretion and a significant decrease in the insulin action compared with the normoglycemic state in the same patients. Recurrence of hyperglycemia in the previously normoglycemic insulin-resistant patients was not associated with any additional change in the already impaired insulin action (34). It is not unreasonable to believe that the African-Americans in our study comprised patients with both the insulin-sensitive and the insulin-resistant variants. It is possible that at least a subgroup of these patients, after achieving improved glycemic control during the study, had improved glucose effectiveness.

There is a great heterogeneity in glucose and insulin metabolism in NIDDM, even between and within ethnic groups. Acknowledgment of these differences may provide greater insight into the pathogenesis, complications, and responses to various pharmacological therapies in subpopulations of diabetic patients. Moreover, because new drugs are becoming available for treatment of NIDDM, it will be useful to assess ethnic differences in response to these modalities based on the knowledge of pathophysiological differences in patients with NIDDM.

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