Ethnicity, Race, and Baseline Retinopathy Correlates in the Veterans Affairs Diabetes Trial

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OBJECTIVE — The Veterans Affairs Diabetes Trial (VADT) cohort is enriched with ~20% Hispanics and 20% African Americans, affording a unique opportunity to study ethnic differences in retinopathy.

RESEARCH DESIGN AND METHODS — Cross-sectional analyses on the baseline seven-field stereo fundus photos of 1,283 patients are reported here. Diabetic retinopathy scores are grouped into four classes of increasing severity: none (10–14), minimal nonproliferative diabetic retinopathy (NPDR) (15–39), moderate to severe NPDR (40–59), and proliferative diabetic retinopathy (60+). These four groups have also been dichotomized to none or minimal (10–39) and moderate to severe diabetic retinopathy (40+).

RESULTS — The prevalence of diabetic retinopathy scores >40 was higher for Hispanics (36%) and African Americans (29%) than for non-Hispanic whites (22%). The difference between Hispanics and non-Hispanic whites was significant ($P < 0.05$). Similarly, the prevalence of diabetic retinopathy scores >40 was significantly higher in African Americans than in non-Hispanic whites ($P < 0.05$). These differences could not be accounted for by an imbalance in traditional risk factors such as age, duration of diagnosed diabetes, HbA_{1c} (A1C), and blood pressure. Diabetic retinopathy severity scores were also significantly associated with increasing years of disease duration, A1C, systolic and diastolic blood pressure, the degree of microalbuminuria, fibrinogen, and the percentage of patients with amputations. There was no relationship between retinopathy severity and the percentage of people who had strokes or cardiac revascularization procedures. There was an inverse relationship between retinopathy severity and total cholesterol, triglycerides, and plasminogen activator inhibitor-1 as well as with smoking history. Diabetic retinopathy scores were not associated with age.

CONCLUSIONS — In addition to many well-known associations with retinopathy, a higher frequency of severe diabetic retinopathy was found in the Hispanic and African-American patients at entry into the VADT that is not accounted for by traditional risk factors for diabetic retinopathy, and these substantial ethnic differences remain to be explained.

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Intensive glycemic control has been shown to decrease the onset and/or progression of retinopathy, nephropathy, and neuropathy in persons with type 1 and type 2 diabetes (1–3). Whether macrovascular complications are similarly affected by blood glucose has not been shown in prospective fashion. It is the aim of the Veterans Affairs Diabetes Trial (VADT) to determine the effect of excellent glycemic control on macrovascular risk in people with advanced diabetes in whom treatment with oral hypoglycemic agents and/or insulin already had failed.

In addition to macrovascular disease at entry, patients in the VADT are evaluated for microvascular complications including retinopathy. Furthermore, almost 20% of the cohort is Hispanic and an additional 20% is African American. Such a large and ethnically diverse group of type 2 individuals affords a unique opportunity to study diabetic retinopathy in various ethnic groups. Several reports have addressed the question of whether there is increased prevalence of retinopathy in Hispanics and African Americans compared with non-Hispanic whites with inconsistent results (see CONCLUSIONS and Table 5). With mydriatic seven-field stereo fundus photographs taken on 1,283 individuals in VADT, important new data are now available to address this issue. Information on the baseline fundus photographs forms the basis of this report.

RESEARCH DESIGN AND METHODS

— The design of VADT has been reported elsewhere (4). Patients consented to a set of seven-field standard stereoscopic color photographs of both eyes, according to the Diabetes Retinopathy Study protocol at baseline and at the end of the study. The Fundus Photograph Reading Center of the University of Wis-

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Abbreviations: NPDR, nonproliferative diabetic retinopathy; PAI, plasminogen activator inhibitor; PDR, proliferative diabetic retinopathy; VADT, Veterans Affairs Diabetes Trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline demographic and risk factor rates by fundus severity score categories*

	Fundus severity score						
Retinopathy	None	Minimal NPDR	Moderate to severe NPDR	PDR	Below median	Above median	*P* value*
Score	10–14	15–39	40–59	60+	10–39	40+	
Patients (*n*)	485	511	208	79	996	287	NS
Hispanic (%)	17	17	25	35	17	28	<0.05
Non-Hispanic white (%)	67	62	50	47	64	49	<0.01
African American (%)	16	19	24	20	17	23	<0.05
Age (years)	60	61	60	61	60	60	NS
Duration of diabetes (years)	7	12	14	17	10	15	<0.05
Smoking (years)	26	26	23	24	26	23	<0.05
A1C (%)	9.3	9.4	9.7	9.4	9.3	9.6	<0.05
Fasting glucose (mg/dl)	189	191	196	193	190	195	NS
UACR (mg/g)	48	123	198	159	87	187	<0.01
Hypertension (%)	72	71	74	80	72	76	NS
Systolic blood pressure (mmHg)	129	133	136	136	131	136	<0.05
Diastolic blood pressure (mmHg)	76	76	78	76	76	77	NS
Amputation (%)	0.8	2.5	3.8	3.8	1.7	3.8	<0.05
Stroke (%)	5.2	6.1	5.8	3.8	5.6	5.2	NS
Cardiac revascularization %	16	25	20	22	21	20	NS
Triglycerides (mg/dl)	242	205	196	176	223	190	<0.05
Total cholesterol (mg/dl)	188	188	185	182	188	184	NS
LDL cholesterol (mg/dl)	108	112	111	108	110	110	NS
HDL cholesterol (mg/dl)	39	39	40	39	39	39	NS
Fibrinogen (mg/dl)	421	383	384	384	402	384	NS
PAI-1	48	43	43	35	45	41	<0.05

*All comparisons are between combined fundus severity scores above the median compared to those below the median. UACR, urine albumin-to-creatinine ratio.

consin assessed the photographs using the Airlie House modified classification and the Early Treatment Diabetic Retinopathy Study severity scale, used in the Veterans Affairs Cooperative Study in Diabetes Mellitus that preceded the current long-term VADT (5).

This report uses retinopathy severity scores for the worse eye in 1,283 patients photographed at baseline. Retinopathy scores are grouped into four classes of increasing retinopathy severity as follows: none (10–14), minimal nonproliferative diabetic retinopathy (NPDR) (15–39), moderate to severe NPDR (40–59), and proliferative diabetic retinopathy (PDR) (60+). In additional analyses, these four groups have also been dichotomized to no or minimal NPDR (10–39) and moderate to severe NPDR or PDR (40+). Ethnicity was self-defined by the patients. Other demographic and biochemical parameters have been described (4). Cardiovascular history was taken at baseline by patient recall and supplemented by review of available VA records.

Statistical analysis

Statistical significance between rates for patients with retinopathy severity scores above or below the median was determined by χ^2 and *Z* tests at the 5% and 1% level.

RESULTS — A total of 1,792 patients in 20 medical centers were randomized into the study. Baseline fundus photographs were obtained in 17 centers for the completed 1,283 patients reported here. Another two patients had both eyes ungradeable, six were not read because of incomplete photos, and seven could not be photographed because of photophobia. Retinopathy was present in 62% of the cohort (798 of 1,283); 40% had minimal NPDR (score 15–39), 16% had moderate NPDR (score 40–59), and 6% had PDR (score 60+) (Table 1).

Table 1 shows baseline risk factor rates for 1,283 patients (97% male) by the four retinopathy score groups, further collapsed into two groups, one with patients below the median and the other with patients above the median. The percentage of Hispanics below the median (that is, with less severe retinopathy) was 17%, less than that above the median (that is, with more severe retinopathy) at 28% ($P < 0.05$). The percentage of African Americans with retinopathy severity scores below the median (17%) was lower than that of patients with scores above the median (23%) ($P < 0.05$). In contrast to the Hispanics and African Americans, the percentage of non-Hispanic whites with retinopathy scores below the median (64%) was higher than the percentage with scores above the median (49%) ($P < 0.01$).

Duration of diabetes, HbA_{1c} (A1C), microalbuminuria (urine albumin-to-creatinine ratio), systolic blood pressure, and lower extremity amputations were positively associated with higher retinopathy scores. Years of smoking, serum triglyceride levels, and concentration of plasminogen activator inhibitor (PAI)-1 were inversely associated. There was no statistically significant association between retinopathy score groups and age, fasting glucose, the diagnosis of hypertension, diastolic blood pressure, standard lipid parameters (except for triglycerides), fibrinogen, or the percentage of patients who had strokes or cardiac revascularization procedures.

Table 2 shows the relationship between the severity of baseline risk factors and the presence of severe retinopathy (>40). Each of the risk factors in the table is grouped into four quartiles of the baseline risk factor and dichotomized into scores above or below the median. The percentage of patients with fundus scores >40 is computed for each cell. For example, 8% of the patients in the lowest duration quartile had fundus scores >40 compared with 42% in the highest duration quartile. Patients with below-median duration have a 12% rate of severe fundus scores >40 compared with a 35% rate for patients with above-median duration. This large difference is statistically significant ($P < 0.01$). Analysis of the data in this manner confirms most of the relationships indicated in Table 1. However, new associations became apparent. There was a significant association with higher fasting blood glucose, diastolic blood pressure, and serum fibrinogen levels with increasing retinopathy severity.

Table 3 presents baseline fundus severity and other risk factor rates by race/

Table 2—*Percent of fundus severity scores >40 by baseline risk factor*

Baseline risk factor	Quartiles (lowest to highest) 1	2	3	4	Quartiles (grouped around the median) 1–2	3–4	*P* value*
Age	22	19	26	22	21	24	NS
Duration of diabetes	8	16	28	42	12	35	<0.01
Smoking	24	24	15	15	24	15	<0.01
HbA_{1c}	17	19	26	28	18	27	<0.01
Fasting glucose	20	17	24	24	19	24	<0.05
UACR	14	15	24	38	15	31	<0.01
Systolic blood pressure	16	23	21	29	20	25	<0.05
Diastolic blood pressure	20	19	27	24	19	25	<0.05
Triglycerides	25	24	17	23	25	20	<0.05
Total cholesterol	23	24	18	23	24	20	<0.05
LDL cholesterol	25	21	20	24	23	22	NS
HDL cholesterol	21	20	25	24	20	25	NS
Fibrinogen	18	21	23	29	20	26	<0.05
PAI-1	23	31	18	21	26	19	<0.01

Data are percentage of patients who have fundus severity scores >40. For example, 8% of the patients in the lowest duration quartile have fundus scores >40 compared with 42% in the highest duration quartile. *All comparisons are between the percentages above the median compared with those below the median. UACR, urine albumin-to-creatinine ratio.

ethnicity. Overall, Hispanics and African Americans had higher baseline rates of severe retinopathy (>40) than non-Hispanic whites ($P < 0.05$). There was some risk factor imbalance among ethnic groups. Both Hispanics and African Americans had higher A1C and diastolic blood pressures than the non-Hispanic whites ($P < 0.05$). In addition, the African Americans had higher systolic blood pressure and LDL cholesterol than the non-Hispanic whites ($P < 0.05$).

To determine whether the race/ethnicity differences in retinopathy severity were a consequence of the unequal presence of these risk factors, the race/ethnic comparisons between non-Hispanic whites and the other ethnic groups were made within "low" and "high" strata of A1C, systolic and diastolic blood pressures, and LDL cholesterol values (Table 4). Statistical significances of the differences were tested by χ^2 or *t* tests. Hispanics and African Americans had higher rates of fundus scores >40 in all strata, indicating that the differences in retinopathy severity were not explained by differences in these factors. Neither variation in diabetes duration nor degree of microalbuminuria could account for the ethnic differences (Tables 1 and 2).

The paradoxical relationship between increased retinopathy severity and decreased years of smoking was also seen when Hispanic and African Americans were compared with non-Hispanic whites in that, despite a higher prevalence of more severe retinopathy, there was a shorter history of years smoking ($P < 0.05$). Although the prevalence of severe retinopathy was substantially lower in non-Hispanic whites, the percentage of non-Hispanic whites that underwent revascularization procedures was double that of Hispanic or African American patients ($P < 0.05$). The non-Hispanic whites, although having a lower frequency of severe retinopathy, were older than their Hispanic or African American counterparts ($P < 0.05$). Serum triglyceride levels were significantly higher in the non-Hispanic whites than in the Hispanic or African-American groups ($P < 0.05$), and plasma PAI-1 levels were significantly higher in non-Hispanic whites than in African Americans ($P < 0.05$).

CONCLUSIONS — The most intriguing finding was that severe retinopathy was more frequent in Hispanics and African Americans than in non-Hispanic whites. These differences did not appear to be explained by age, duration of diagnosed diabetes, A1C, or other standard risk factors. Another substudy from the VADT also found ethnic differences in Hispanics, who had lower cardiovascular disease and arterial calcification than non-Hispanic whites not explained by either standard or novel risk factors (6).

Table 3—*Fundus severity scores and retinopathy risk factors by ethnic group*

	Non-Hispanic white	Hispanic	African American	Other	All patients	*P* value*
Patients (*n*)	779	236	240	28	1283	NS
Fundus severity (% >40)	22	36	29	18	26	<0.05
Age (years)	61	58	58	59	60	<0.05
Duration of diabetes (years)	11	11	11	12	11	NS
Smoking (years)	27	21	24	27	26	<0.05
A1C (%)	9.2	9.7	9.8	9.1	9.4	<0.05
Fasting glucose (mg/dl)	195	191	179	193	191	<0.05
Hypertension (%)	71	71	78	86	72	NS
Systolic blood pressure (mmHg)	130	130	136	130	131	<0.05
Diastolic blood pressure (mmHg)	74	78	80	74	76	<0.05
UACR (mg/g)	101	106	131	194	109	NS
Cardiac revascularization (%)	26	12	12	25	21	<0.05
Total cholesterol (mg/dl)	186	189	188	192	187	NS
Triglycerides (mg/dl)	239	204	151	190	215	<0.05
LDL cholesterol (mg/dl)	107	110	118	109	110	<0.05
HDL cholesterol (mg/dl)	38	39	43	42	39	<0.05
Fibrinogen (mg/dl)	370	374	368	367	370	NS
PAI-1	46	49	33	48	44	<0.05

*All comparisons are between non-Hispanic white and the other ethnic groups. UACR, urine albumin-to-creatinine ratio.

Table 4—*Percent of fundus severity scores >40 by ethnicity stratified by risk factors*

	Non-Hispanic white	Hispanic	African American	Other	All patients
Systolic blood pressure					
<140 mmHg	17	30	22	14	20
≥140 mmHg	21	38	35	29	28
Diastolic blood pressure					
<80 mmHg	18	35	23	11	21
≥80 mmHg	19	28	31	33	24
A1C					
<9.1%	16	24	20	19	18
≥9.1%	21	36	32	17	26
LDL cholesterol					
<100 mg/dl	17	31	27	40	21
≥100 mg/dl	19	32	28	6	23

Data are percentages of patients with fundus severity scores >40.

Ethnic differences in retinopathy were found in some, but not all, of the other epidemiologic studies (Table 5). In the San Antonio Heart Study and National Health and Nutrition Examination Survey III, Hispanics had an adjusted twofold increased risk of severe retinopathy compared with non-Hispanic whites (7,8). In a recent review of eight epidemiologic studies of 4,440 persons with diabetes of whom 1,415 were Hispanic, retinopathy was found more frequently in Hispanics (9). In contrast, in the San Luis Valley Diabetes Study, the incidence, progression, and prevalence of diabetic retinopathy were lower in Hispanics than in non-Hispanic whites (10,11). In a study of Mexican Americans in Arizona, the prevalence of diabetic retinopathy was no different in non-Hispanic whites than in other populations (12).

VADT is the first study to use seven-field photos in dilated eyes to report increased retinopathy prevalence in African Americans than in non-Hispanic whites not accounted for by differences in other risk factors. Other studies have used nonmydriatic photos. In the Maryland Diabetes Visual Impairment Project, the prevalence of retinopathy in African Americans was similar to that of non-Hispanic whites (13). However, in a subsequent survey in a smaller sample, 50% of the African Americans versus only 19% of the non-Hispanic whites developed retinopathy at an average follow-up of 4 years, not accounted for by differences in risk factors (14). There was also a 46% increase in the prevalence of retinopathy in African Americans in the National Health and Nutrition Examination Survey III cohort, not significant after adjustment for risk factors (7). Of the 4,440 diabetic person database examined by The Eye Diseases Prevalence Research Group (9), 615 were black and did not show an increase in the prevalence of retinopathy. However, all of these 615 individuals were from the Caribbean Barbados Eye Study, and their genetic makeup might be different from that of African Americans. The findings of the VADT support continued careful examination of the possibility that African Americans may have an increased incidence of eye disease.

Our data show that there is an inverse association of levels of PAI-1 with retinopathy severity in concert with several smaller studies (15,16). Fibrinogen levels were higher in patients with severe retinopathy in VADT, similar to some but not all other studies (17,18).

In our cohort, glycemia was associated with retinopathy severity, in keeping with much epidemiologic and clinical trial evidence (1,2,7,8,10–12,14,19,20). Retinopathy severity was associated with blood pressure in VADT. There are many epidemiologic studies on the relationship between blood pressure and the incidence and progression of retinopathy, and some data are conflicting (7,8,10, 11,13,19,20). The relationship is supported by therapeutic intervention showing reduced retinopathy progression with decreasing blood pressure (21,22). In the VADT, a mean blood pressure of 126/74 mmHg is reported (23). Retinopathy severity increased with duration of diabetes, consistent with many epidemiologic studies and the association between the presence and severity of diabetic retinopathy and albuminuria is known (7,8,11–14,19,20).

The inverse relationship between duration of smoking and retinopathy severity was unexpected. In the San Luis Valley Diabetes Study, cigarette smoking correlated with lower prevalence of retinopathy only for those taking insulin (11). There was no association between smoking and retinopathy in National Health and Nutrition Examination Survey III (7) or in the Maryland Diabetes Visual Impairment Project (13).

In the Early Treatment Diabetic Retinopathy Study, higher baseline total and LDL cholesterol increased twofold the risk of retinal hard exudates or macular edema (24) and the risk of visual loss by 50%. Similar findings occurred in a subgroup of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (25). Other studies have found no association (7). Our data suggested that there was an inverse association between eye disease and

Table 5—*Ethnicity and diabetic retinopathy*

Ethnicity	Study (ref.)	*n*	Method	Retinopathy
Hispanics	NHANES III (7)	939	Nonmydriatic photos	Increased
	Colorado (11)	279	3-field photos	Decreased
	Colorado (11)	143	3-field photos	Equal
	Arizona (12)	1,044	3-field photos	Equal
	San Antonio (8)	313	7-field photos	Increased
	VADT*	1,283	7-field photos	Increased
African Americans	Maryland (13)	1,428	Nonmydriatic photos	Equal
	Maryland (14)	105	Nonmydriatic photos	Increased
	NHANES III (7)	939	Nonmydriatic photos	Equal
	VADT*	1,283	7-field photos	Increased

*Current study.

total cholesterol and triglycerides. This paradoxical relationship might be explained by prevalent treatment of dyslipidemia in this cohort (26).

VADT will provide vital information on factors affecting retinopathy in established type 2 diabetes optimally treated for other risk factors and complications of diabetes. Unlike previous studies in large populations, it intends to provide data on ethnic differences in the complications of this heterogeneous disease. Ultimately, the VADT will show the prospective risk-to-benefit ratio of intensive glycemic control in a population that continues to present glycemic treatment dilemmas (27).

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