# Development of Proliferative Diabetic Retinopathy in African-Americans and Whites With Type 1 Diabetes

CYNTHIA L. ARFKEN, PHD
PHILIP L. RENO, AB
JULIO V. SANTIAGO, MD†
RONALD KLEIN, MD, MPH

**OBJECTIVE** — To investigate the comparable risk of developing proliferative diabetic retinopathy (PDR) in African-Americans and whites with type 1 diabetes.

**RESEARCH DESIGN AND METHODS** — Using a cohort design with the sample drawn from medical records, the sample consisted of 312 people with type 1 diabetes (97 African-Americans, 215 whites) having at least two visits to a Model Demonstration Unit with gradeable fundus photographs (stereo, color, 7 standard fields). Excluded were subjects with preexisting or treated PDR or hemoglobinopathy. Masked grading of the fundus photographs was conducted at the Wisconsin Reading Center.

**RESULTS** — At baseline, African-Americans had poorer glycemic control (mean $HbA_1$ of 11.3 vs. 10.0%, $P < 0.0001$), higher systolic blood pressure (mean of 117 vs. 110 mmHg, $P < 0.001$), and were older (mean of 26.8 vs. 19.3 years, $P < 0.0001$) than the white subjects. African-Americans also tended to have slightly longer duration of diabetes and length of follow-up. In the African-Americans, 17.5% developed PDR, compared with 10.2% in the 215 whites, for an odds ratio (OR) of 1.86 (95% CI 0.93–3.70). When adjusted for baseline glycemic control, retinopathy grade, and length of follow-up, race was not a significant risk factor (OR = 0.73, 95% CI 0.30–1.78).

**CONCLUSIONS** — African-Americans with type 1 diabetes may have a higher rate of developing PDR. The observed racial difference, however, is attributable to the presence of a worse risk factor profile, especially to poorer glycemic control. Efforts should be expanded to improve the care for all individuals with poor glycemic control.

African-Americans with diabetes are at an increased risk for developing nephropathy (1) and requiring lower-limb amputations (2). There are, however, limited data comparing the risk of developing another microvascular complication, proliferative diabetic retinopathy (PDR), in African-Americans and other racial or ethnic groups, although at least one study is currently underway (3). Our pilot study (4) had suggested that African-Americans with type 1 diabetes in our sample had poorer glycemic control and increased mean blood pressure, both of which would be associated with heightened development of diabetic retinopathy (5–10), than the whites with type 1 diabetes. The rate of developing retinopathy or the progression of preexisting retinopathy was unexpectedly similar, however, thus yielding an adjusted protective effect of race. That study suffered from having a small sample size and limited follow-up time. Thus, it did not examine the time span in which vision is threatened with the more clinically significant end point of PDR. Therefore, the current study was undertaken to examine the comparable risk of developing PDR in African-Americans and whites with type 1 diabetes.

## RESEARCH DESIGN AND METHODS

— Similar to our pilot study (4), data were obtained by reviewing records of subjects participating in the Model Demonstration Units of the Washington University (St. Louis, MO) Diabetes Research and Training Center, and masked grading of their fundus photographs was carried out at the Wisconsin Reading Center (Madison, WI). Subjects participating in the Model Demonstration Units are recruited from the private practices of family practice physicians, internists, and pediatricians in the St. Louis metropolitan area and from the Washington University Endocrinology and Diabetes Clinics. Of the subjects participating in the Model Demonstration Units, ~59% have repeat visits. These subjects have diverse socioeconomic and educational backgrounds and varying degrees of diabetic control, complications, and regimen adherence.

After giving informed consent, subjects undergo a detailed history and physical examination, followed by extensive testing using a standardized protocol designed to characterize the status of diabetic complications. Information on socioeconomic and educational background is not systematically collected. For this analysis, the variables examined include supine blood pressure (after a 5-min rest), serum creatinine concentration (measured by the Jaffe reaction), and glycosylated hemoglobin (detailed below). To determine retinopathy status, color stereoscopic fundus photographs of seven standard fields are taken after pupillary dilation. Subjects also undergo an assessment and an update of diabetes knowledge and skills by a clinical nurse specialist and a registered dietitian. Results and recommended adjustments in the therapeutic regimen are then communicated to the subject and primary physician.

Criteria for inclusion in this analysis were as follows: *1*) type 1 diabetes (defined as age of onset of ≤40 years and continuous insulin usage), *2*) at least two visits with

From the Department of Internal Medicine (C.L.A., P.L.R., J.V.S.); the Division of Biostatistics (C.L.A.); the Department of Pediatrics (J.V.S.), Washington University School of Medicine, St. Louis, Missouri; and the Department of Ophthalmology and Visual Sciences (R.K.), University of Wisconsin Medical School, Madison, Wisconsin.

Address correspondence and reprint requests to Cynthia L. Arfken, PhD, Psychiatry-9B UHC, 4201 St. Antoine, Detroit, MI 48201. E-mail: carfken@med.wayne.edu.

Received for publication 13 October 1997 and accepted in revised form 15 January 1998.

†Deceased August 1997.

**Abbreviations:** OR, odds ratio; PDR, proliferative diabetic retinopathy.

**Table 1—*Baseline comparisons***

| | African-American subjects | White subjects | *P* values |
|---|---|---|---|
| *n* | 97 | 215 | — |
| Factors | | | |
| $HbA_1$ (%) | 11.3 ± 2.8 | 10 ± 2.1 | 0.0001 |
| Age (years) | 27 ± 15 | 19 ± 11 | 0.0001 |
| Retinopathy status (%) | | | |
| None | 53 | 60 | 0.0001 |
| Minimal/mild | 17 | 18 | — |
| Moderate/severe | 31 | 23 | — |
| Systolic blood pressure (mmHg) | 117 ± 19 | 110 ± 16 | 0.002 |
| Females (%) | 68 | 55 | 0.03 |
| Serum creatinine (mg/dl) | 0.79 ± 0.25 | 0.74 ± 0.18 | 0.04 |
| Follow-up (years) | 7.2 ± 3.1 | 6.7 ± 3.0 | 0.12 |
| Duration (years) | 9.2 ± 7.0 | 8.0 ± 6.4 | 0.15 |

Data are means ± SD or %.

gradeable eye photographs, and 3) race recorded as African-American or white. If there were more than two visits, visits were chosen to maximize the time of follow-up. Initially, age between 7 and 41 years at baseline with gradeable eye photographs was a criterion for inclusion, as was duration of diabetes of ≤16 years, to make the sample similar to those used in the Diabetes Control and Complications Trial (10). However, these latter two criteria were relaxed to expand the number of African-Americans in the sample. Subjects with hemoglobinopathy were excluded because one of the assays used to measure glycosylated hemoglobin is inaccurate in the presence of hemoglobinopathies. Subjects with either PDR or evidence of treatment for PDR at the baseline were also excluded.

From 1978 to mid-1981, glycosylated hemoglobin was measured as $HbA_{1c}$ by high-performance liquid chromatography (11). From mid-1981 through late 1987, glycosylated hemoglobin was measured as $HbA_1$ by minicolumn cation-exchange chromatography (Isolab, Akron, OH). Before changing to the minicolumn assay in mid-1981, glycosylated hemoglobin was determined simultaneously by the two procedures (high-performance liquid chromatography and minicolumn) in 121 subjects with diabetes by our clinical laboratory, and the following relationship was found: $HbA_1$ (minicolumn) = 0.786 $HbA_{1c}$ ± 1.9 ($r$ = 0.92) (12). The corresponding 95% CI is approximately ±0.2%. In late 1987, the assay for glycosylated hemoglobin was changed to measure total glycosylated hemoglobin by boronate affinity chromatography (GlycoTest, Pierce Chemical, Rockford, IL). Before changing assays in 1987, glycosylated hemoglobin was determined simultaneously by the two procedures ($HbA_1$ by minicolumn and total glycosylated hemoglobin by affinity chromatography) in 56 subjects with diabetes by our clinical laboratory, and the following relationship was found: $HbA_1$ (minicolumn) = 0.567 total glycosylated hemoglobin by affinity chromatography ± 2.15 ($r$ = 0.87) (13). Consistency of measurement over time has been accomplished by standardization against high-performance liquid chromatography methods (14).

All measures of glycosylated hemoglobin in this study are expressed in units equivalent to $HbA_1$ by cation-exchange minicolumn, either as originally measured or as converted by the regression equations discussed above. The normal range of $HbA_1$ in our clinical laboratory is from 4.6 to 5.7%.

The color stereoscopic fundus photographs of seven standard fields were sent to the Wisconsin Reading Center for masked grading. Retinopathy status was determined using the scale developed for the Wisconsin Epidemiologic Study of Diabetic Retinopathy (15). Briefly, the scale measures no retinopathy; minimal, mild, moderate, or severe nonproliferative retinopathy; and proliferative retinopathy, treated or untreated. Each eye is graded separately. The grades of both eyes are then combined, with the more severely involved eye receiving greater weight, to form an ordinal scale with 11 levels of increasing severity. For this analysis, the primary end point was development of PDR, which was defined as a reading consistent with PDR or evidence of prior treatment for PDR. The secondary end point of a two-step or more progression on the ordinal scale, compared with those who had progressed only one step, had no change, or regressed, was also examined. Those subjects who had progressed to PDR were considered to have progressed two steps or more for this secondary end point.

Analysis consisted of comparing those who developed PDR or were treated for it with those who had not developed it using stepwise multivariate logistic regression to control for length of time between visits and potential confounders. Similar analysis was then conducted for the development of two steps or more of progression. This secondary

**Table 2—*Factors associated with development of PDR***

| | PDR | No PDR | *P* values |
|---|---|---|---|
| *n* | 39 | 273 | — |
| Factors | | | |
| $HbA_1$ (%) | 12.0 ± 2.2 | 10.2 ± 2.4 | 0.0001 |
| Age (years) | 27 ± 14 | 21 ± 12 | 0.005 |
| Retinopathy status (%) | | | |
| None | 23 | 62 | 0.0001 |
| Minimal/mild | 8 | 19 | — |
| Moderate/severe | 69 | 19 | — |
| Systolic blood pressure (mmHg) | 120 ± 21 | 111 ± 16 | 0.01 |
| Females (%) | 64 | 58 | 0.49 |
| Serum creatinine (mg/dl) | 0.79 ± 0.22 | 0.75 ± 0.20 | 0.20 |
| Follow-up (years) | 8.3 ± 2.9 | 6.6 ± 3.0 | 0.001 |
| Duration (years) | 11.6 ± 6.0 | 7.9 ± 6.6 | 0.001 |
| African-Americans (%) | 44 | 29 | 0.07 |

Data are means ± SD or %.

**Table 3—*Multivariate analysis***

| | OR (95% CI) | *P* values |
|---|---|---|
| Factors | | |
| Retinopathy status | | |
| None/minimal/mild | 1.00 (—) | 0.0001 |
| Moderate/severe | 12.40 (5.31–28.98) | — |
| $HbA_1$ (2% change) | 1.92 (1.36–2.70) | 0.0002 |
| Follow-up (5 years) | 3.50 (1.78–6.90) | 0.0003 |
| African-Americans | 0.73 (0.30–1.78) | 0.49 |

analysis was included with the intention to replicate our pilot study (4). Results are expressed as odds ratios (ORs) with large sample 95% CIs. For continuous variables, ORs were calculated using a change of 1 SD for the entire sample. Comparisons at baseline between African-Americans and whites and bivariate comparisons of those developing PDR were conducted using *t* tests and Mann-Whitney *U* tests for continuous variables and $\chi^2$ for categorical variables.

**RESULTS** — The sample included 97 African-Americans and 215 whites with type 1 diabetes. At baseline, the African-American subjects had significantly poorer glycemic control, higher systolic blood pressure, and higher serum creatinine than the white subjects (Table 1). The African-American subjects were also older than the white subjects. Mean duration of diabetes and mean years between visits were in the direction of increased risk among the African-American subjects.

Of the African-American subjects, 17.5% developed PDR, compared with 10.2% in the white subjects, for an OR of 1.86 (95% CI 0.93–3.70). Other factors associated in bivariate analysis with the development of PDR were poorer glycemic control, older age at baseline, more advanced retinopathy at baseline, higher systolic blood pressure, increased duration of diabetes, and increased follow-up interval (Table 2).

To assess the independent risk factors for development of PDR, stepwise logistic regression analysis was conducted. This analysis confirmed that more advanced retinopathy at baseline, poorer glycemic control, and increased follow-up interval independently predicted development of PDR (Table 3). The statistical interaction of glycemic control and more advanced retinopathy at baseline was nonsignificant (*P* = 0.88) and not included in the final model. To assess the impact of these three remaining factors on race as a risk factor, race was forced into the resulting model. This analysis yielded a substantially reduced and nonsignificant OR of 0.73 (95% CI 0.30–1.78).

Using the factors identified above as independent predictors of PDR, race-specific models were constructed (Table 4). Although based on small numbers in the African-American group, the resulting ORs for retinopathy at baseline, glycemic control, and follow-up interval by race had overlapping CIs.

Analysis was then repeated using the secondary end point of a two-step or more progression in retinopathy. The African-American subjects had a trend towards higher rate of progression (56 vs. 46%, *P* = 0.11). In multivariate analysis, length of follow-up (OR = 3.50, 95% CI 1.78–6.90) and glycemic control (OR = 1.92, 95% CI 1.36–2.70) were independent predictors of a two-step or more progression in retinopathy. However, race and more advanced retinopathy at baseline were not predictive of progression. Forcing race into the multivariate analysis yielded an OR of 0.93 (95% CI 0.53–1.63).

**CONCLUSIONS** — The African-Americans in our sample had a worse risk factor profile for the development of PDR than the whites in our sample. As expected, this resulted in a trend toward a greater rate of developing PDR in the African-American subjects. When controlling for the presence of other risk factors, however, race clearly did not predict development of PDR. Thus, the appearance of a higher rate of developing PDR was not due to race but to the presence of other risk factors. This study was not designed to answer the equally important question of why the African-American subjects had a higher burden of risk factors at baseline.

The results, while consistent with findings for other microvascular complications (1,2), contradict our earlier findings of an adjusted protective effect (4). The current findings are based on both a larger sample size and a longer follow-up interval, lending more credence to the conclusions. Interestingly, we found identical findings regardless of whether we used PDR or a two-step or more progression as the end point.

The current study does share a number of limitations with the earlier study. First, neither study used a population-based sample. Thus, we cannot conclude that African-Americans with type 1 diabetes in general have a worse risk profile than whites; we can conclude that the African-Americans with type 1 diabetes who have repeat visits at our Model Demonstration Unit had a worse risk factor profile than similarly selected whites. We demonstrated

**Table 4—*Race-specific multivariate analysis***

| | *n* | OR (95% CI) | *P* value |
|---|---|---|---|
| Factors | | | |
| African-American subjects | 97 | | |
| Retinopathy status | | | |
| None/minimal/mild | | 1.00 (—) | — |
| Moderate/severe | | 6.68 (1.75–25.42) | 0.005 |
| $HbA_1$ (2% change) | | 1.68 (1.00–2.85) | 0.05 |
| Follow-up (5 years) | | 4.90 (1.48–16.90) | 0.009 |
| White subjects | | | |
| Retinopathy status | 215 | | |
| None/minimal/mild | | 1.00 (—) | — |
| Moderate/severe | | 16.55 (5.43–50.45) | 0.0001 |
| $HbA_1$ (2% change) | | 2.17 (1.34–3.50) | 0.002 |
| Follow-up (5 years) | | 2.84 (1.19–6.81) | 0.02 |

previously that the white subjects were similar to those in the Wisconsin Epidemiologic Study of Diabetic Retinopathy sample, a population-based sample (4,16). Different selection process by race (i.e., selection bias), while possible, seems unlikely to explain the findings but is always a concern when the sample is not population-based and information is not available on everyone.

Second, the sample size, while larger, is still too small for rigorous analysis. With a larger sample size, we would have been able to stratify the subjects by extent of retinopathy at baseline. In addition, the race-specific analysis conducted could only describe trends in risk factors for African-American subjects although the trends were similar to those for the white subjects. Both a larger sample size and a population-based sample would have enhanced the generalizability of the results.

Third, the study's conclusions are limited to subjects with type 1 diabetes. Potential racial differences in the risk of developing PDR for people with type 2 diabetes are very important, and unpublished data suggest a finding similar to that of this study (M.I. Harris, M. Rowland, R.K., C.C. Cowie, D.D. Byrd-Holt, unpublished observations).

Our findings do support efforts to reduce the presence and extent of risk factors for PDR, regardless of race. Glycemic control was equally important in the white subjects and the African-American subjects. In that respect, the findings of the Diabetes Control and Complications Trial would appear applicable to African-Americans with type 1 diabetes too (10).

In conclusion, African-Americans with type 1 diabetes may have a higher rate of developing PDR. The observed racial difference, however, is at least partially attributable to the presence of a worse risk factor profile of, most notably, poor glycemic control. Efforts should be expanded in improving the care in those individuals with poorer glycemic control.

**Acknowledgments**— This work was supported by a grant from the American Diabetes Association and in part by National Institutes of Health Grants P60-DK20579, M01-RR00036, M01-RR06021, and R01-EY03083.

This study was presented in part at the Annual Meeting of the American Diabetes Association, Boston, Massachusetts, June 1997.

**References**

1. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM: Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N Engl J Med* 321:1074–1079, 1989
2. Most RS, Sinnock P: The epidemiology of lower extremity amputations in diabetic individuals. *Diabetes Care* 6:87–91, 1983
3. Roy MD, Borenstein M: Risk factors for diabetic retinopathy in African-Americans with type 1 diabetes: the New Jersey Study (Abstract). *Invest Ophthalmol Vis Sci* 38 (Suppl.):S235, 1997
4. Arfken CL, Salicrup AE, Meuer SM, Del Priore LV, Klein R, McGill JB, Rucker CS, White NH, Santiago JV: Retinopathy in African Americans and whites with insulin-dependent diabetes mellitus. *Arch Intern Med* 154:2597–2602, 1994
5. Knowler WC, Bennett PH, Ballintine EJ: Increased incidence of retinopathy in diabetics with elevated blood pressure. *N Engl J Med* 302:645–650, 1980
6. Rand LI, Krolewski AS, Aiello LM, Warram JH, Baker RS, Maki T: Multiple factors in the prediction of risk of proliferative diabetic retinopathy. *N Engl J Med* 313:1433–1438, 1985
7. Ballard DJ, Melton LJ III, Dwyer MS, Trautmann JC, Chu CP, O'Fallon WM, Palumbo PJ: Risk factors for diabetic retinopathy: a population-based study in Rochester, Minnesota. *Diabetes Care* 9:334–342, 1986
8. Krolewski AS, Warram JH, Rand LI, Christlieb AR, Busick EJ, Kahn CR: Risk of proliferative diabetic retinopathy in juvenile-onset type 1 diabetes: a 40-years follow-up study. *Diabetes Care* 9:443–452, 1986
9. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL: Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. *JAMA* 260:2864–2871, 1988
10. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
11. Davis JE, McDonald JM, Jarrett L: A high-performance liquid chromatography method for hemoglobin A1c. *Diabetes* 27:102–107, 1978
12. Hammons GT, Junger K, McDonald JM, Ladenon JH: Evaluation of three minicolumn procedures for measuring hemoglobin A1. *Clin Chem* 28:1775–1778, 1982
13. Nahm MH, Cryer P, Clutter W, Santiago JV: A new assay method for glycated hemoglobin. *Barnes Hosp Dv Lab Med Newslett* 10:1–5, 1987
14. Bodor GS, Little RR, Garrett M, Brown W, Goldstein DE, Nahm MH: Standardization of glycohemoglobin determinations in the clinical laboratory: 3 years of experience *Clin Chem* 38:2414–2418, 1992
15. Klein R, Klein BEK, Magli YL, Brothers RJ, Meuer SM, Moss SE, Davis MD: An alternative method of grading diabetic retinopathy. *Ophthalmology* 93:1183–1187, 1986
16. Klein R, Klein BEK, Moss SE, DeMets DL, Kaufman I, Voss PS: Prevalence of diabetes mellitus in southern Wisconsin. *Am J Epidemiol* 119:54–61 1984