P-selectin Plasma Levels and Genetic Variant Associated With Diabetic Retinopathy in African Americans

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• PURPOSE: To report the prevalence and risk factors for retinopathy in African Americans with impaired fasting glucose (IFG) and type 2 diabetes in the Jackson Heart Study and to determine if P-selectin plasma levels are independently associated with retinopathy in this population.
• DESIGN: Prospective, cross-sectional observational study.
• METHODS: SETTING: Community-based epidemiologic study. STUDY POPULATION: Total of 629 patients with type 2 diabetes and 266 participants with impaired fasting glucose. OBSERVATION PROCEDURES: Bilateral, 7-field fundus photographs were scored by masked readers for diabetic retinopathy (DR) level. Covariate data including P-selectin plasma levels and genotypes were collected in a standardized fashion. MAIN OUTCOME MEASURES: Association between risk factors, including P-selectin plasma levels and genotypes, and retinopathy.
• RESULTS: The prevalences of any retinopathy among participants with IFG and type 2 diabetes were 9.4% and 32.4%, respectively. Among those with type 2 diabetes, in multivariate models adjusted for age, sex, and other traditional risk factors, higher P-selectin levels were associated with any DR (odds ratio = 1.11, 95% confidence interval = 1.02–1.21, $P = .02$) and proliferative DR (odds ratio = 1.23, 95% confidence interval = 1.03–1.46, $P = .02$). To further investigate the relationship between P-selectin and DR, we examined the association between P-selectin genotype and DR. Minor allele homozygotes for the variant rs6128 were less likely to develop DR (P after Bonferroni correction = 0.03).
• CONCLUSIONS: Both serologic and genetic data show an association between P-selectin and DR in the Jackson Heart Study. If confirmed in other studies, this association may provide insight into the pathogenesis of retinopathy. (Am J Ophthalmol 2015;159(6): 1152–1160. © 2015 by Elsevier Inc. All rights reserved.)

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DIABETES IS THE LEADING CAUSE OF BLINDNESS among working-age adults in the United States.[1] There is evidence that diabetic retinopathy (DR) is more prevalent in African Americans than in non-Hispanic whites.[2,3] Epidemiologic and clinical studies have provided information regarding DR in African Americans with type 2 diabetes.[2–10] Some of these studies were performed over 20 years ago when diabetes treatment options were limited and patients had poorer glycemic control. Many of these studies only used 1 or 2 photographic fields to ascertain DR. Limited-field photography can lead to inaccurate DR grading as compared with dilated 7-field fundus photography.[11] Nonmydriatic limited-field photographs are also more likely to be ungradable.[12,13] Studies have shown that subjects with ungradable photographs are more likely to have characteristics consistent with increased retinopathy risk and be African Americans.[6,7] Therefore, retinopathy may be underascertained in African Americans, particularly when a limited number of fields are photographed without pharmacologic pupil dilation.[14]

Longer diabetes duration, hyperglycemia, and hypertension are consistent risk factors for DR,[10] and there are other putative risk factors for DR. Hyperlipidemia and obesity impact DR in some, but not all, studies.[15–19] Increased urinary albumin has been associated with retinopathy in some populations.[20,21] C-reactive protein has not been a biomarker for DR in most studies,[22,23] but a recent prospective investigation found an association with macular edema.[24] P-selectin and E-selectin are molecules involved in leukocyte recruitment and rolling and platelet adhesion. A genetic association between variants in the P-selectin gene, *SELP*, and DR has been reported in white subjects.[25]

Impaired fasting glucose is defined as a fasting plasma glucose between 100 and 125 mg/dL. Retinopathy develops in 7%–10% of impaired fasting glucose patients,[26–29] and blood pressure and body mass index have been identified as risk factors for retinopathy in Europeans with impaired fasting glucose.[26] There is limited information regarding retinopathy prevalence and risk factors in African Americans with impaired fasting glucose.[27]

The purpose of our study was to estimate the prevalence of and identify risk factors for retinopathy ascertained with

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7-field, dilated fundus photography in African Americans with impaired fasting glucose and type 2 diabetes from the Jackson Heart Study. In particular, we were interested in whether there was an association between P-selectin plasma levels and genotype and retinopathy.

METHODS

ALL ASPECTS OF THIS CROSS-SECTIONAL OBSERVATIONAL study were prospectively approved by the Institutional Review Boards at the University of Mississippi Medical Center and Massachusetts Eye and Ear Infirmary. All participants provided written informed consent. The study was compliant with the regulations of the Health Insurance Portability and Accountability Act.

The Jackson Heart Study is a community-based observational study of cardiovascular disease among African Americans living in Mississippi.[30] Standardized phenotyping protocols have measured physical characteristics at the 2004 baseline examination and subsequent examinations (Examination 2 in 2005-08 and Examination 3 in 2009-12).[31] We established an ancillary retinopathy study that ran concurrently with Examination 3. Jackson Heart Study participants with type 2 diabetes or impaired fasting glucose were invited to participate in the ancillary study. Diabetes was defined as (a) taking antidiabetic medication or (b) meeting the hemoglobin A1c or fasting plasma glucose criteria for diabetes diagnosis.[32] Type 2 diabetes was defined as age at diabetes diagnosis ≥30 years. Impaired fasting glucose was defined as specified above.

Enrolled participants had 1 study visit at the University of Mississippi Medical Center Department of Ophthalmology. A short questionnaire about ocular history and diabetes diagnosis was administered. Bilateral, dilated, 7-standard-field fundus photographs including macular stereoscopic pairs were obtained with a TRC-50DX camera (Topcon, Tokyo, Japan). The photographs were scored contemporaneously by 2 independent, masked ophthalmologist-investigators with the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.[33] Clinically significant macular edema was deemed present if ETDRS criteria were met and/or if focal laser treatment scars were present.[33] Disagreements were arbitrated by a third masked ophthalmologist-investigator and/or by joint review by the ophthalmologist-investigators. Participants were excluded only if they had another ocular disease that precluded photograph grading.

Quality metrics for contemporaneous and temporal reproducibility were assessed. Intergrader agreement was measured in terms of percentage agreement and weighted kappa. The contemporaneous intergrader exact agreement percentages for ETDRS grade and presence of clinically significant macular edema were 96.3% and 96.8%, respectively. The associated weighted kappas were 0.76 and 0.52, respectively. One hundred photographs graded in the first year were randomly selected and regraded at the study's end with readers masked to original grade assigned. For these regraded photographs, the percentages of exact agreement between the grades assigned in the first year and last year of the study were 95.5% and 94.0%, respectively, for ETDRS grade and presence of clinically significant macular edema. The corresponding weighted kappas were 0.84 and 0.48, respectively. These metrics suggest there was no systematic temporal drift in evaluating ETDRS grade and presence of clinically significant macular edema.

• **COVARIATE DATA:** Covariates were chosen because of association in other populations and data availability from Jackson Heart Study examinations.[30] The risk factors considered were: age, sex, hemoglobin A1c, diabetes duration, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, C-reactive protein, urine albumin, smoking status, diabetic medication use, E-selectin, and P-selectin.

Covariate data were selected from the Jackson Heart Study examination closest to the retinopathy study visit for which the participant had available data. Diabetes duration was calculated from the onset date to the retinopathy examination date. Seated blood pressure was measured 3 times and the mean was used in the analyses. Smoking status was defined as ever having smoked (current or past smoker) vs never having smoked. Urine albumin was obtained from a spot urine specimen. Diabetic medication use was defined as taking any diabetic medication. Plasma E-selectin and P-selectin were quantified by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota, USA). The interassay coefficients of variation for the E-selectin and P-selectin detection methods were 9.78% and 5.14%, respectively. A subset of patients in the Jackson Heart Study had been genotyped as part of a larger consortium for several vascular disease candidate genes, as previously described.[34] This list of candidate genes included 3 single nucleotide polymorphisms in *SELP*: rs6128, rs6133, and rs3917779.

• **STATISTICAL METHODS:** Retinopathy status was based on the eye with the higher ETDRS level. Absence of retinopathy was defined as ETDRS level <14. We examined 3 different outcomes: any retinopathy (ETDRS level ≥14), proliferative DR (ETDRS level ≥60), and clinically significant macular edema. Clinically significant macular edema was deemed present if at least 1 eye demonstrated clinically significant macular edema and/or focal laser scars. If 1 eye was ungradable, the scores for the other eye were used to define these outcomes.

We estimated the prevalence of any retinopathy in impaired fasting glucose participants and of any retinopathy, proliferative diabetic retinopathy (PDR), and clinically

significant macular edema in type 2 diabetes participants. We examined risk factors in participants in our ancillary study compared with those who did not participate. Univariate analyses comparing participants with and without any retinopathy were performed separately for impaired fasting glucose and type 2 diabetes participants. For type 2 diabetes participants, univariate analyses comparing participants (1) with PDR (ETDRS level ≥60) and without PDR (ETDRS level <60) and (2) with and without clinically significant macular edema were also performed. Differences in means and proportions were tested by the *t* test and χ^2 test, respectively. We used the subset of participants with complete information for the covariate of interest in that particular analysis to maximize generalizability and power.

To examine the association between risk factors and retinopathy, we constructed multivariate models using backward stepwise logistic regression to determine the odds ratios and 95% confidence intervals. All models were adjusted for age and sex. A *P* value <.05 was considered statistically significant. For the genetic analyses of the association between single nucleotide polymorphisms in *SELP* and retinopathy, the χ^2 test was used to compare the frequency of minor allele homozygotes between cases and controls. The Bonferroni method was used to correct for multiple hypothesis testing. All analyses were performed using Stata/IC version 12.1(Stata, College Station, Texas, USA).

RESULTS

FROM JACKSON HEART STUDY EXAMINATIONS 1 AND 2, WE identified 1303 type 2 diabetes participants and 689 impaired fasting glucose participants. A total of 629 type 2 diabetes and 266 impaired fasting glucose participants enrolled in the retinopathy study. Table 1 compares known DR risk factors between enrolled and nonenrolled participants. Enrolled impaired fasting glucose participants had a higher mean age and lower mean diastolic blood pressure. On average, enrolled type 2 diabetes participants had shorter diabetes duration, lower hemoglobin A1c, and lower systolic blood pressure.

The distribution of retinopathy grades is shown in Table 2. The prevalences of any retinopathy in impaired fasting glucose and type 2 diabetes participants were 9.4% and 32.4%, respectively. No impaired fasting glucose participants had clinically significant macular edema. Among type 2 diabetes participants, 48 (7.8%) had clinically significant macular edema and 28 (4.5%) had PDR. In impaired fasting glucose participants, none of the examined covariates were associated with retinopathy in univariate or multivariate analyses.

In type 2 diabetes participants, longer diabetes duration, higher hemoglobin A1c, higher systolic blood pressure, greater waist circumference, higher urine albumin, diabetic medication use, and higher plasma P-selectin levels were associated with retinopathy in univariate analyses (Table 3). In the multivariate model (Table 4), P-selectin levels remained significantly associated with presence of any retinopathy when controlling for other risk factors, including C-reactive protein, another inflammatory biomarker. The odds of having retinopathy were 71% higher for every additional 5 years of diabetes ($P = 5.7 \times 10^{-13}$), 25% higher for each percentage point increase in hemoglobin A1c ($P = .002$), 13% higher for every 10 mm Hg increase in systolic blood pressure ($P = .03$), 2-fold higher for those using a diabetic medication ($P = .04$), and 11% higher for each 5 ng/mL increase in plasma P-selectin ($P = .02$). Because higher P-selectin levels have been associated with cardiovascular events in other populations,[35] we examined whether inclusion of history of a cardiovascular event (defined as coronary heart disease, stroke, or heart failure) in the model would alter the association of P-selectin levels with presence of retinopathy, but this did not alter the results, with higher P-selectin levels remaining significantly associated with retinopathy despite adjusting for cardiovascular events ($P = .01$).

Results for the univariate analyses for PDR are shown in Table 3. Older age, longer diabetes duration, higher hemoglobin A1c, higher body mass index, larger waist circumference, lower diastolic blood pressure, lower total cholesterol, lower low-density lipoprotein cholesterol, higher urine albumin, diabetic medication use, and higher P-selectin were associated with PDR. In the multivariate model, P-selectin remained significantly associated with PDR (Table 5). The odds of having PDR were more than 2-fold higher for every 5-year increase in duration of diabetes ($P = 3.8 \times 10^{-8}$), 26% higher for every 10 mm Hg increase in systolic blood pressure ($P = .03$), 23% higher for each 5 ng/mL increase in plasma P-selectin ($P = .02$), and 2% lower for every mg/dL increase in total cholesterol ($P = .01$). Again the association between P-selectin and retinopathy remained significant after controlling for history of cardiovascular events.

Longer diabetes duration, higher hemoglobin A1c, lower diastolic blood pressure, higher urine albumin, and diabetic medication use were associated with clinically significant macular edema in univariate analyses (Table 3). In the multivariate regression model, diabetes duration and hemoglobin A1c remained significantly associated. The odds of having clinically significant macular edema were 68% higher for each 5-year increase in duration of diabetes (odds ratio = 1.68, 95% confidence interval = 1.42–2.00, $P = 1.3 \times 10^{-9}$) and 37% higher for every hemoglobin A1c percentage point (odds ratio = 1.37, 95% confidence interval = 1.15–1.63, $P = .001$).

To further explore the association of P-selectin with DR, we examined the association between the 3 variants in the *SELP* gene and the presence of DR. Table 6 shows the results of association testing between *SELP* genotypes and DR. Participants without retinopathy were more likely to be minor allele homozygotes (TT) for rs6128 than those

TABLE 1. Risk Factors in Jackson Heart Study Participants who Enrolled vs Did Not Enroll in the Diabetic Retinopathy Study

	Enrolled in Retinopathy Study		Not Enrolled in Retinopathy Study		
Variable	N	% or Mean (SD)	N	% or Mean (SD)	*P* Value
Impaired fasting glucose participants					
Age, y	266	65.7 (9.6)	423	63.0 (12.4)	.003
Percent female	266	59.8%	423	52.7%	.07
Hemoglobin A_{1C}, %	266	5.9 (0.38)	422	5.9 (0.58)	.34
Body mass index, kg/m^2	266	31.3 (6.0)	422	32.3 (7.0)	.06
Waist circumference, cm	266	102.6 (13.6)	423	104.1 (16.0)	.20
Systolic BP, mm Hg	266	128.5 (16.6)	423	130.8 (18.9)	.11
Diastolic BP, mm Hg	266	74.6 (9.9)	423	76.8 (11.1)	.01
Total cholesterol, mg/dL	266	199.3 (37.3)	423	202.1 (39.8)	.36
Triglycerides, mg/dL	266	103.4 (65.7)	423	102.5 (58.3)	.86
LDL cholesterol, mg/dL	266	121.1 (34.4)	422	125.9 (37.3)	.09
HDL cholesterol, mg/dL	266	57.6 (17.5)	423	55.8 (16.5)	.16
C-reactive protein, mg/L	266	4.4 (5.3)	423	5.5 (11.0)	.12
Urine albumin, mg/L	259	33.7 (119.3)	391	39.0 (152.5)	.64
Ever smoked, %	266	26.6%	423	29.3%	.35
Type 2 diabetes participants					
Age, y	629	66.5 (10.1)	674	66.4 (11.0)	.95
Percent female	629	66.1%	674	66.3%	.94
Diabetes duration, y	629	9.6 (9.0)	655	12.0 (9.8)	7.4×10^{-6}
Hemoglobin A_{1C}, %	623	7.2 (1.6)	668	7.5 (1.8)	.002
Body mass index, kg/m^2	627	34.1 (6.9)	674	34.0 (7.5)	.89
Waist circumference, cm	627	109.0 (15.2)	673	109.1 (16.2)	.94
Systolic BP, mm Hg	627	130.0 (20.2)	674	132.9 (21.1)	.01
Diastolic BP, mm Hg	627	73.6 (11.1)	674	74.1 (11.7)	.44
Total cholesterol, mg/dL	612	188.9 (44.6)	642	190.3 (46.2)	.58
Triglycerides, mg/dL	612	112.2 (65.4)	642	123.5 (145.2)	.07
LDL cholesterol, mg/dL	612	111.7 (39.6)	632	113.6 (40.7)	.42
HDL cholesterol, mg/dL	612	54.7 (14.8)	642	53.4 (14.9)	.12
C-reactive protein, mg/L	626	5.5 (7.9)	672	5.4 (9.1)	.81
Urine albumin, mg/L	610	150.2 (621.5)	583	146.8 (526.5)	.92
Ever smoked, %	625	33.0%	673	33.1%	.95
Diabetic medication use	624	78.2%	667	80.7%	.28

BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

with retinopathy ($P = .03$). To investigate whether this result might be influenced by differences in the genotype distribution in the overall Jackson Heart Study participant population by glycemic status (no diabetes vs impaired fasting glucose vs type 2 diabetes) we examined rs6128 genotype among these 3 groups using the χ^2 test. There was no significant difference among these groups in rs6128 genotype distribution ($P = .84$). There was also no significant difference in rs6128 genotype distribution between type 2 diabetes participants who chose to enroll in the retinopathy ancillary study and those who did not ($P = .42$). We also examined the association between P-selectin levels and *SELP* genotypes for these 3 variants. Minor allele homozygotes at rs6128 had lower mean P-selectin levels than major allele carriers (25.8 ng/mL vs 34.5 ng/mL, $P = .046$). There were no significant associations between P-selectin plasma levels and *SELP* genotypes for rs6133 and rs3917779.

DISCUSSION

OUR ANCILLARY STUDY OF DR IN THE JACKSON HEART Study provides information about retinopathy and its risk factors in African Americans with impaired fasting glucose and type 2 diabetes using gold-standard 7-field fundus photography in the era of enhanced options for glycemic control. We confirmed the well-established risk factors for DR—increased duration of diabetes, poor glycemic control, and hypertension—in the Jackson Heart Study. In addition, we have found a novel association between P-selectin plasma levels and DR in this African American cohort, as well as an association between P-selectin genotype and presence of retinopathy.

When we compare our study's 9.4% retinopathy prevalence in African Americans with impaired fasting glucose with that reported for other ethnic groups with impaired fasting glucose, we find the results to be consistent. Studies

TABLE 2. Distribution of Diabetic Retinopathy Grades Among Impaired Fasting Glucose and Type 2 Diabetes Participants in the Jackson Heart Study

Worst Eye ETDRS Grade	Impaired Fasting Glucose Participants (Mean Age = 65.7 Years)	Type 2 Diabetes Participants (Mean Age = 66.5 Years)
Unable to grade	1	6
≤14	240	421
15	12	31
20	9	50
35	4	76
43	0	11
47	0	4
53	0	2
71	0	27
81	0	1
Total	266	629

ETDRS = Early Treatment Diabetic Retinopathy Study.

of white and Asian subjects with impaired fasting glucose have found retinopathy prevalences of 10% and 10.3%, respectively.[26,28] One study of participants with impaired fasting glucose and/or impaired glucose tolerance, another prediabetic state, found a 6.7% retinopathy prevalence.[29] The Diabetes Prevention Program, which included multiple ethnicities, found a 7.9% retinopathy prevalence among participants with impaired fasting glucose and/or impaired glucose tolerance.[27] Our data reinforce that retinopathy can develop in some patients before the onset of overt type 2 diabetes.

We did not find any traditional DR risk factors, P-selectin, or E-selectin to be associated with retinopathy in impaired fasting glucose participants. One study found increased blood pressure and body mass index to be risk factors for retinopathy in Europeans with impaired fasting glucose,[26] but this has not been seen by other investigators.[29] The lack of an association with blood pressure, body mass index, and other risk factors could be explained by the limited number of impaired fasting glucose participants with retinopathy (n = 25) or by varying risk factor profiles in different populations.

When we compare the 32.4% retinopathy prevalence in type 2 diabetic participants in this study with that reported in African Americans in other relatively recent studies, the results are also consistent. In the Veterans Affairs Diabetes Trial, published in 2005, the retinopathy prevalence was 29% among African Americans.[36] In the Multi-Ethnic Study of Atherosclerosis, published in 2006, African Americans had a retinopathy prevalence of 37%.[8] In the National Health and Nutrition Examination Survey 2005–2008 study, the crude DR prevalence was 38.8% among non-Hispanic blacks.[2] Of note, the participants who enrolled in our ancillary study were more likely to have better glycemic control, shorter diabetes duration, and lower systolic blood pressure than those who did not enroll. Since these are significant retinopathy risk factors in our cohort, it is likely that the DR prevalence in the entire group of Jackson Heart Study type 2 diabetes participants is higher. The prevalences of PDR and clinically significant macular edema in the Jackson Heart Study are also in line with those observed in other populations.[8,10]

The presence of any DR in the type 2 diabetes participants was associated with longer diabetes duration, poorer glycemic control, and higher systolic blood pressure. This is consistent with other studies of DR in type 2 diabetes.[2,5–8,10] Longer duration of diabetes and higher systolic blood pressure were associated with PDR but hemoglobin A1c was not. This same lack of association between hemoglobin A1c and PDR has been found in a Latino population.[19] The association between hemoglobin A1c and DR may weaken with more advanced forms of retinopathy. One explanation for this phenomenon is that the diagnosis of PDR can be the impetus for tighter blood sugar control. Patients with PDR may be motivated to achieve better hemoglobin A1c levels after receiving this diagnosis and their hemoglobin A1c after PDR diagnosis may be not be reflective of their glycemic control for the majority of the duration of their diabetes.

In the univariate analyses, we found that higher plasma P-selectin levels were associated with DR and PDR. These associations remained significant in the multivariate models that controlled for both C-reactive protein, another measure of inflammation, and cardiovascular events, which have been associated with higher P-selectin levels. P-selectin is a protein that functions as a cell adhesion molecule on the surface of activated endothelial cells and platelets. Previous studies have not found an independent association between P-selectin and DR,[37,38] but these studies were smaller than the current investigation. Other lines of evidence also suggest P-selectin could play a role in DR. P-selectin is found in fibrovascular membranes removed from patients with PDR.[39] An association between single nucleotide polymorphisms in the gene that encodes P-selectin, *SELP*, and DR was previously found in white subjects, although it has not been independently replicated.[25] In the current study we found an association between 1 of these single nucleotide polymorphisms, rs6128, and presence of any DR in African Americans. The direction of effect was the same as in white subjects with the minor allele, T, conferring a decreased risk of DR. The previous study had looked at this SNP in African Americans from other cohorts, including a small subset of the participants from the Jackson Heart Study, and did not find the association.[25] Most of the African Americans in the cohorts used in the previous study were phenotyped with a limited number of nondilated fields in each eye, which may have contributed to the null findings. In the current study, we verified that there were no differences in the rs6128 genotype distribution in Jackson Heart Study participants by glycemic status or in participants who

TABLE 3. Risk Factors in Type 2 Diabetes Jackson Heart Study Participants With and Without Any Diabetic Retinopathy, Proliferative Diabetic Retinopathy, and Clinically Significant Macular Edema (Univariate Analyses)

	Any Retinopathy (ETDRS Grade ≥14)					Proliferative Diabetic Retinopathy (ETDRS Grade ≥60)					Clinically Significant Macular Edema				
	No Retinopathy		Retinopathy			No PDR		PDR			No CSME		CSME		
Variable	N	% or Mean (SD)	N	% or Mean (SD)	*P* Value[a]	N	% or Mean (SD)	N	% or Mean (SD)	*P* Value[a]	N	% or Mean (SD)	N	% or Mean (SD)	*P* Value[a]
Age, y	421	66.6 (9.9)	202	65.8 (10.4)	.31	595	66.2 (10.0)	28	70.2 (9.9)	.04	571	66.2 (9.9)	48	67.5 (11.0)	.38
Percent female	421	64.6%	202	69.8%	.20	595	65.9%	28	75.0%	.32	571	66.5%	48	64.6%	.78
Diabetes duration, y	421	6.8 (6.9)	202	15.3 (10.1)	1.5×10^{-31}	595	8.8 (8.1)	28	26.7 (9.2)	4.7×10^{-27}	571	8.6 (8.2)	48	20.5 (10.1)	6.0×10^{-20}
Hemoglobin A_{1C}, %	415	6.9 (1.2)	202	7.9 (1.9)	3.5×10^{-14}	589	7.2 (1.6)	28	7.8 (1.7)	.03	565	7.1 (1.5)	48	8.2 (2.0)	2.4×10^{-6}
Body mass index, kg/m^2	419	33.8 (7.0)	202	34.6 (6.4)	.17	593	34.0 (6.8)	28	36.7 (7.0)	.04	569	34.0 (6.8)	48	34.6 (6.9)	.56
Waist circumference, cm	419	108.2 (15.4)	202	111.0 (14.7)	.03	593	108.7 (14.9)	28	117.4 (19.0)	.003	569	108.8 (15.0)	48	112.4 (16.6)	.11
Systolic blood pressure, mm Hg	419	128.7 (18.4)	202	132.4 (23.4)	.03	593	129.7 (19.8)	28	134.9 (28.3)	.18	569	129.8 (20.1)	48	132.3 (22.2)	.42
Diastolic blood pressure, mm Hg	419	74.0 (10.3)	202	72.9 (12.5)	.23	593	73.9 (10.9)	28	69.2 (13.1)	.03	569	74.0 (10.9)	48	70.3 (12.4)	.03
Total cholesterol, mg/dL	412	190.0 (42.9)	194	186.5 (48.2)	.37	579	189.6 (44.6)	27	171.8 (41.6)	.04	556	189.0 (44.0)	46	191.2 (51.6)	.74
Triglycerides, mg/dL	412	110.2 (62.4)	194	116.6 (71.6)	.27	579	112.0 (65.9)	27	117.7 (56.4)	.66	556	112.6 (66.8)	46	106.8 (48.9)	.57
LDL cholesterol, mg/dL	412	112.9 (39.3)	194	109.2 (40.3)	.29	579	112.5 (39.6)	27	95.3 (35.5)	.03	556	111.9 (39.0)	46	113.1 (45.9)	.85
HDL cholesterol, mg/dL	412	55.0 (15.2)	194	54.1 (13.9)	.46	579	54.8 (14.9)	27	53.0 (12.3)	.54	556	54.6 (14.9)	46	56.8 (12.5)	.33
C-reactive protein, mg/L	418	5.9 (8.7)	202	4.9 (5.9)	.13	592	5.5 (8.0)	28	6.4 (5.0)	.55	568	5.6 (8.2)	48	4.8 (4.5)	.47
Urine albumin, mg/L	412	88.0 (424.6)	193	283.3 (901.3)	.0003	581	135.8 (595.8)	24	502.1 (1064.8)	.005	555	131.0 (579.3)	46	393.0 (1013)	.006
Ever smoked	418	33.2%	201	31.0%	0.59	592	32.3%	27	37.0%	.60	568	32.0%	47	38.3%	.38
Diabetic medication use	416	70.2%	202	94.6%	6.2×10^{-12}	590	77.1%	28	100%	.004	566	76.3%	48	97.9%	.001
E-selectin, ng/mL	393	47.7 (23.8)	189	48.7 (24.5)	0.16	556	46.8 (24.2)	26	43.4 (19.9)	.47	531	46.5 (24.5)	47	46.9 (18.5)	.91
P-selectin, ng/mL	393	32.8 (12.2)	189	36.6 (13.2)	0.0007	556	33.8 (12.5)	26	38.9 (15.7)	.04	531	33.7 (12.6)	47	37.3 (12.8)	.06

CSME = clinically significant macular edema, ETDRS = Early Treatment Diabetic Retinopathy Study; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PDR = proliferative diabetic retinopathy.

[a] *t* test for continuous variables, χ^2 test for dichotomous variables.

TABLE 4. Risk Factors for Any Diabetic Retinopathy in Type 2 Diabetes Participants in the Jackson Heart Study: Results of Multivariate Analyses Controlling for Age and Sex

Variable	OR (95% CI)	*P* Value
Diabetes duration, y[a]	1.71 (1.48–1.98)	5.7×10^{-13}
Hemoglobin A_{1C}, %	1.25 (1.08–1.44)	.002
Systolic blood pressure, mm Hg[b]	1.13 (1.01–1.25)	.03
Diabetic medication use	2.14 (1.04–4.38)	.04
P-selectin, ng/mL[c]	1.11 (1.02–1.21)	.02

CI = confidence interval; OR = odds ratio.

[a]Odds ratio calculated per 5-year increase in duration of diabetes.

[b]Odds ratio calculated per 10 mm Hg increase in systolic blood pressure.

[c]Odds ratio calculated per 5 ng/mL increase in P-selectin level.

TABLE 5. Risk Factors for Proliferative Diabetic Retinopathy in Type 2 Diabetes Participants in the Jackson Heart Study: Significant Results in Multivariate Analyses Controlling for Age and Sex

Variable	OR (95% CI)	*P* Value
Diabetes duration, y[a]	2.19 (1.66–2.89)	3.8×10^{-8}
Systolic blood pressure, mm Hg[b]	1.26 (1.02–1.57)	.03
P-selectin, ng/mL[c]	1.23 (1.03–1.46)	.02
Total cholesterol, mg/dL	0.98 (0.969–0.996)	.01

CI = confidence interval; OR = odds ratio.

[a]Odds ratio calculated per 5-year increase in duration of diabetes.

[b]Odds ratio calculated per 10 mm Hg increase in systolic blood pressure.

[c]Odds ratio calculated per 5 ng/mL increase in P-selectin level.

TABLE 6. Association Between *SELP* Genotype and Presence of Any Diabetic Retinopathy in the Jackson Heart Study

	No Retinopathy		Retinopathy		
SELP SNP	N	% Minor Allele Homozygotes	N	% Minor Allele Homozygotes	*P* Value[a]
rs6128 (C/T)	174	5.7%	102	0%	.03
rs6133 (A/C)	135	19.3%	71	16.9%	.68
rs3917779 (A/G)	135	24.4%	50	26.8%	.72

SNP = single nucleotide polymorphism.

[a]Corrected for multiple hypothesis testing by Bonferroni method.

enrolled in the retinopathy study vs those who did not. This makes it less likely that there are skews in the genotype distribution in the larger or nonenrolled Jackson Heart Study population that would explain the observed association between rs6128 genotype and retinopathy.

We also found an association between *SELP* genotype and P-selectin levels, with major allele carriers having higher plasma P-selectin levels. Higher P-selectin levels may indicate that patients with DR have greater activation of their endothelial cells and platelets than those without DR. More study is required to understand if the elevated P-selectin levels are an initiating event in DR pathogenesis or whether they are a downstream product of a higher propensity for microvascular damage in these patients. The association between *SELP* genotype, P-selectin levels, and DR status suggest it is possible that P-selectin levels have an upstream effect on DR development.

The strengths of this study include the excellent phenotyping with dilated, 7-field retinal photography; the largest single sample of African Americans with type 2 diabetes and retinopathy data to date; and novel data on impaired fasting glucose and retinopathy in African Americans. There are also limitations to our study. Mydriatic retinal photography is the most effective DR detection strategy, with a higher sensitivity than ophthalmoscopy.[40] However, ideally, photography could be supplemented with ophthalmoscopy for cases where photographs are ungradable,[40] but we did not have ophthalmoscopic data available. A reading center was not used for photograph grading, but readers were ophthalmologists and quality metrics indicated high intergrader agreement and no significant temporal drift in severity grading. Focal laser scars were used as a criterion to ascertain clinically significant macular edema and might have falsely increased clinically significant macular edema cases as focal laser could have been performed, depending on the physician's discretion, for microaneurysms threatening the fovea but not actually causing clinically significant macular edema. Because of the varied Jackson Heart Study recruitment methods, the sample is not statistically representative of the population and therefore results are not directly generalizable to all African Americans. Although we had very high rates of completeness for covariate data, these data were not always available from the Jackson Heart Study main examination that was contemporaneous with our ancillary study, and this could introduce some imprecision for detecting associations. The cross-sectional design limits our ability to judge the causal relationships of the associations found. Finally, for the genotype associations, only a subset of participants had consented to genotyping, so the power to detect modest genetic effects was limited.

In summary, we present new data on the retinopathy frequency in African Americans with impaired fasting glucose and updated data on DR prevalence in African Americans with type 2 diabetes in the modern era of increased options for glycemic control. We confirm the associations of DR with longer diabetes duration, hyperglycemia, and

increased systolic blood pressure. We also report a novel association of DR with plasma P-selectin levels, which remained significant after adjustment for other known risk factors, as well as an association between *SELP* rs6128 genotype and presence of DR. Further investigation of these associations in other DR cohorts is required to confirm the potential relationship between P-selectin and retinopathy.

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Biosketch

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Biosketch

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