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Association of Systemic Inflammation With Retinal Vascular Caliber in Patients With AIDS

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Purpose. To evaluate relationships among retinal vascular caliber and biomarkers of systemic inflammation in patients with AIDS.

Methods. A total of 454 participants with AIDS had retinal vascular caliber (central retinal artery equivalent and central retinal vein equivalent) determined from enrollment retinal photographs by reading center graders masked to clinical and biomarker information. Cryopreserved plasma specimens were assayed for inflammatory biomarkers, including C-reactive protein (CRP), IL-6, interferon-γ inducible protein (IP)-10, kynurenine/tryptophan (KT) ratio, and intestinal fatty acid binding protein (I-FABP).

Results. In the simple linear regression of retinal vascular caliber on plasma biomarkers, elevated CRP, IL-6, and IP-10 were associated with retinal venular dilation, and elevated KT ratio with retinal arteriolar narrowing. In the multiple linear regression, including baseline characteristics and plasma biomarkers, AMD was associated with dilation of retinal arterioles (mean difference: 9.1 μm; 95% confidence interval [CI] 5.2, 12.9; $P < 0.001$) and venules (mean difference, 10.9 μm; 95% CI, 5.3, 16.6; $P < 0.001$), as was black race ($P < 0.001$). Hyperlipidemia was associated with retinal venular narrowing (mean difference, −7.5 μm; 95% CI, −13.7, −1.2; $P = 0.02$); cardiovascular disease with arteriolar narrowing (mean difference, −5.2 μm; 95% CI, −10.3, −0.1; $P = 0.05$); age with arteriolar narrowing (slope, −0.26 μm/year; 95% CI, −0.46, −0.06; $P = 0.009$); and IL-6 with venular dilation (slope, 5.3 μm/standard deviation $\log_{10}$[plasma IL-6 concentration]; 95% CI, 2.7, 8.0; $P < 0.001$).

Conclusions. These data suggest that retinal vascular caliber is associated with age, race, AMD, hyperlipidemia, cardiovascular disease, and selected biomarkers of systemic inflammation.

Keywords: retinal vascular caliber, inflammation, AIDS

Human immunodeficiency virus (HIV)-infected persons treated with modern antiretroviral therapy (ART) have suppressed HIV replication, reduced amounts of HIV RNA circulating in the blood (HIV viral load), improved immune function typically manifested as a rise in CD4+ T cells (immune recovery), decreased opportunistic infections, and an improved lifespan.[1–4] Nevertheless, they have a shortened lifespan compared to comparably aged HIV-uninfected persons, largely due to age-related diseases.[5,6] They have an increase is age-related diseases such as cardiovascular disease, metabolic disorders (e.g., diabetes and osteoporosis), neurocognitive decline, and age-related cancers not associated with AIDS,[7–10] suggesting accentuated and accelerated aging.[9,10] They also exhibit features of immunosenescence, a state characterized by chronic immune activation and systemic inflammation, but a poor response to new antigenic challenges.[9–12] Compared to HIV-uninfected persons, those with HIV infection have persistently high levels of immune activation and systemic inflammation, despite ART-mediated viral suppression, particularly those who initiate ART at advanced stages of HIV disease.[13–15]

Consistent with this accentuated/accelerated aging, persons with AIDS have an ∼4-fold increased age- and sex-adjusted prevalence of intermediate-stage AMD compared to HIV-uninfected persons[16] and a ∼1.75-fold increased race/ethnicity- and sex-adjusted incidence of intermediate-stage AMD compared to HIV-uninfected persons.[17] Retinal vascular caliber declines with age, and persons with AIDS have retinal arteriolar and venular calibers comparable to HIV-uninfected persons ∼10 years older.[18] Although a decline in retinal vascular caliber is associated with increasing age, persons with AIDS and AMD have dilated retinal arterioles and venules compared to persons with AIDS without AMD.[19] Retinal venular dilation is associated with systemic inflammation in HIV-uninfected persons.[20–24]

Elevated blood levels of C-reactive protein (CRP) a biomarker of systemic inflammation, are a risk factor for the development of AMD in HIV-uninfected persons,[25] and persons with AMD have elevated blood levels of several proinflammatory cytokines,[26] suggesting that systemic inflammation might be a common pathogenetic factor in both processes. Therefore, we evaluated the relationship between several biomarkers of systemic inflammation and retinal vascular caliber in persons with AIDS enrolled in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA).

Patients and Methods

The Longitudinal Study of the Complications of AIDS was a prospective cohort study of patients with the acquired immunodeficiency syndrome conducted in the era of modern ART.[27] Baseline photographs were taken on all participants and evaluated for retinal vascular caliber at the Reading Center in the Department of Ophthalmology and Visual Sciences at the University of Wisconsin, Madison, School of Medicine and Public Health by graders masked as to clinical data, as previously described.[18,19,28] As part of a study of AMD, mortality, and biomarkers of systemic inflammation, participants with AMD at enrollment were matched on decade of age, race/ethnicity-, and sex with 2 controls from LSOCA for a case control study,[29] resulting in a study population of 454 persons with AIDS. Retinal vascular indices were determined using previously-described semi-automated methods. Briefly, the six largest arterioles and six largest venules in a ring-shaped area located between 0.5 and 1.0 disc diameters from the edge of the optic nerve were identified. Computer software measured the caliber of the individual vessels, then combined them into two summary measures: the central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE).[18,19,28] Intermediate-stage AMD was graded at the reading center as previously described.[16,17,19,29]

Phlebotomy was performed at enrollment, and plasma specimens cryopreserved. Cryopreserved specimens were thawed and assayed for biomarkers of inflammation using commercially available immunoassay kits in the Core Immunology Laboratories of the University of California, San Francisco, School of Medicine as previously described.[29,30] Inflammatory biomarkers included high-sensitivity CRP (UBI Magiwel, Mountain View, CA, USA), IL-6 (hsIL-6, R&D Systems, Minneapolis, MN, USA), soluble CD14 (sCD14, R&D Systems), soluble CD163 (sCD163, R&D Systems), and interferon-γ inducible protein (IP)-10 (IP-10, R&D Systems), also known as CXCL10. Intestinal fatty acid binding protein (I-FABP), a marker of impaired gut epithelial integrity (R&D Systems), and plasma kynurenine to tryptophan (KT) ratio, a marker of dendritic cell indoleamine 2,3 dioxygenase (IDO) upregulation,[31] also were assessed. The kynurenine tryptophan (KT) ratio was assayed using liquid chromatography-tandem mass spectrometry.[32]

Statistics

Plasma inflammatory biomarker values were $\log_{10}$ transformed for normality. In order to compare different biomarkers with different dynamic ranges, results were standardized to the standard deviation (SD) units of the $\log_{10}$(biomarker plasma level). Testing of the direct association between inflammatory biomarkers and retinal vascular caliber was performed using simple linear regression and the independent association was tested using multiple linear regression with forward selection using a P value for entry ≤ 0.05 from a candidate set of 18 variables including the seven plasma biomarkers, AMD status, hyperlipidemia, hypertension, diabetes, cardiovascular disease, elevated creatinine, HIV load, CD4+ T-cell count, CD8+ T-cell count, current use and any prior use of ART. Age, race/ethnicity, and sex were forced into the model. Similar results were obtained using backward selection and Bayesian Information Criteria (data not shown). Mean central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) were tested across categoric variables at enrollment using ANOVA. Results for categorical variables are expressed as the mean difference in vascular CRAE or CRVE, whereas results for continuous variable are expressed as the slope and 95% confidence interval (CI) of the regression line for CRAE or CRVE (in μm) per standardized unit of the biomarker. P values were nominal and not adjusted for multiple outcomes or multiple looks. The data analyses were generated using statistical software (SAS version 9.4, SAS Institute Inc., Cary, NC, and StataCorp, Release 15; StataCorp LLC, College Station, TX, USA).

Results

Characteristics of the study population are outlined in Table 1. The relationships between baseline demographic, comorbid disease, HIV treatment, HIV virologic, and immunologic variables and retinal vascular caliber are outlined in Table 2. Age-related macular degeneration was associated with retinal arteriolar and venular dilation. Older age, male sex, white race, hypertension, cardiovascular disease, receiving ART at enrollment, and elevated HIV load all were associated with retinal arteriolar narrowing. Female sex and black race were associated with retinal venular dilation, whereas hyperlipidemia and receiving ART at enrollment were associated with narrower retinal venules. There were no differences in age by race/ethnicity (mean age: white 47.8 years, black 47.8 years, other 46.8 [$P = 0.70$ by ANOVA]). There was a difference in the frequency of hypertension by race/ethnicity (proportion with hypertension: white, 23%; black, 30%; other 15% [$P = 0.03$ by Fisher's exact test]). Although there was a sex difference by race/ethnicity (proportion women: white, 7%; black, 36%; other, 27% [$P < 0.001$]), the frequency of hypertension did not differ by sex (men, 24%; women, 25%). Overall the rate of hypertension did not vary significantly by race/ethnicity and sex (interaction P value = 0.26). Results of linear regression of CRAE and CRVE versus inflammatory biomarker levels are outlined in Table 3 and Figures 1 and 2. Venous dilation was significantly associated with the biomarkers CRP, IL-6, and IP-10. The corresponding slopes (95% CI) of CRVE versus plasma biomarker in μm/standard deviation $\log_{10}$(plasma biomarker concentration) and P values were: CRP = 3.7 (95 CI = 1.4, 6.0), $P = 0.002$; IL-6 = 3.7 (95% CI = 1.6, 5.8), $P = 0.001$; and IP-10 = 2.8 (95% CI = 0.6, 5.0), $P = 0.01$. Conversely, sCD14, sCD163, KT ratio, and I-FABP were not significantly associated with venular caliber. KT ratio was inversely related to CRAE; the slope was −2.0 (95% CI = −3.6, −0.4), $P = 0.02$. In the simple linear regression of biomarkers, no other biomarkers were related to CRAE.

In the multiple linear regression of retinal vascular caliber including baseline characteristics and plasma biomarkers (Table 4), AMD was associated with dilation of retinal arterioles (mean difference 9.1 μm; 95% CI, 5.2, 12.9; $P < 0.001$) and venules (mean difference 10.9 μm; 95% CI, 5.3, 16.6; $P < 0.001$). Black race was associated with retinal arteriolar dilation (mean difference vs. white race 9.7 μm; 95% CI, 5.6, 13.8; $P < 0.001$ and mean difference vs. other race 1.7 μm; 95% CI −3.1, 6.5) and retinal venular dilation (mean difference vs. white race, 12.4 μm; 95% CI, 6.4, 18.4; $P < 0.001$ and mean difference vs. other race, 6.5 μm; 95% CI −0.5, 13.5).

Table 1. Characteristics of the Study Population of Persons with AIDS

Characteristic	Results (n = 454)
Design variable	
Age-related macular degeneration, n (%)	150 (33.0)
No age-related macular degeneration, n (%)	304 (67.0)
Demographics	
Age (y), mean ± SD	43.3 ± 9.9
Sex, n (%)	
Men	351 (77.3)
Women	103 (22.7)
Race, n (%)	
White	180 (39.6)
Black	190 (41.8)
Other	84 (18.5)
Smoking history, n (%)	
Never smoker	146 (38.9)
Former smoker	127 (33.9)
Current smoker	102 (27.2)
Comorbidity, n (%)	
Hypertension	112 (24.7)
Diabetes	40 (8.8)
Hyperlipidemia	97 (21.4)
Cardiovascular disease	58 (15.4)
Renal disease (elevated serum creatinine)	26 (5.7)
HIV treatment, n (%)	
On antiretroviral therapy at enrolment	390 (85.9)
Received antiretroviral therapy at or before enrolment	423 (93.2)
Virology/Immunology	
HIV load ($\log_{10}$(copies/mL))	
Mean + SD	3.2 ± 1.4
Distribution, n (%)	
<2.6	164 (38.8)
>2.6 to 3.0	76 (18.0)
>3.0	183 (43.3)
CD4+ T cells (cells/μL)	
Median (25th, 75th percentile)	214 (93, 361)
Distribution, n (%)	
<100	117 (25.9)
100–199	95 (21.0)
200–499	185 (40.9)
>500	55 (12.2)
Inflammatory biomarkers* (mean +SD)	
CRP ($\log_{10}$[mg/L])	0.33±0.60
IL-6 ($\log_{10}$[pg/mL])	0.34±0.40
IP-10 ($\log_{10}$[pg/mL]))	2.37±0.38
sCD14 ($\log_{10}$[μg/mL]))	0.42±0.12
sCD163 ($\log_{10}$[ng/mL]))	2.82±0.25
KT ratio ($\log_{10}$[ratio])	1.76±0.29
I-FABP ($\log_{10}$[pg/mL])	3.15±0.32

* CRP, C-reactive protein; IL-6, interleukin-6; IP-10, interferon-γ inducible protein-10; sCD14, soluble CD14; sCD163, soluble CD163; KT ratio, kynurenine tryptophan ratio; I-FABP, intestinal fatty acid binding protein.

Hyperlipidemia was associated with retinal venular narrowing (mean difference, −7.5; 95% CI, −13.7, −1.2; P = 0.02). Cardiovascular disease was associated with retinal arteriolar narrowing (mean difference = −5.2 μm; 95% CI −10.3, −0.1; P = 0.05). Age was associated with arteriolar narrowing (slope = −0.26 μm/year; 95% CI, −0.46, -0.06; P = 0.009). Among the inflammatory biomarkers, IL-6 was associated with venular dilation (slope = 5.3 μm/standard deviation $\log_{10}$[plasma IL-6 concentration]; 95% CI, 2.7, 8.0; P < 0.001).

As a sensitivity analysis, the multiple linear regression was performed without AMD in the model. The results (Supplemental Table 1, available online) were similar in direction and magnitude to those with AMD in the model with two exceptions. Without AMD in the model, IL-6 plasma level was associated with retinal arteriolar dilation (slope = 2.1 μm/standard deviation $\log_{10}$[plasma concentration IL-6]; P = 0.03) and cardiovascular disease was not associated with retinal arteriolar narrowing.

The total effect of each biomarker on CRAE and CRVE was tested across various subgroups including AMD status, age, sex, and race. There was no evidence of a significant subgroup interaction effect (P < 0.01) although the power to detect these effects is limited (data not shown).

Discussion

Our data suggest that multiple factors are associated with retinal vascular caliber. Increasing age and cardiovascular disease are associated with retinal arteriolar narrowing, and hyperlipidemia is associated with retinal venular narrowing. Black race is associated with both retinal arteriolar and venular dilation. As previously reported,[19] AMD is associated with both retinal arteriolar and retinal venular dilation. The results for the inflammatory biomarkers are more complex. In the simple linear regression, retinal venular dilation was associated with the inflammatory biomarkers CRP, IL-6, and IP-10. In the multiple linear regression, retinal venular dilation was associated only with elevated plasma levels of IL-6. C-reactive protein is an acute phase reactant, which is elevated in several conditions characterized by systemic inflammation, including infection and autoimmune or auto-inflammatory diseases. In animal models, CRP has been reported to inhibit endothelial nitric oxide synthase (eNOS),[33] plausibly contributing to endothelial dysfunction, atherosclerosis, and retinal vascular caliber. Nevertheless, Mendelian randomization studies cast doubt on a direct causal contribution of CRP to cardiovascular disease in man.[34] IL-6 is a proinflammatory cytokine, secreted by several innate immune cells and B-cells, and it is an inducer of CRP synthesis in the liver.[29,30] The association of retinal venous dilation with both CRP and IL-6 levels in the simple linear regression strengthens the inference that retinal venous dilation is related to systemic inflammation, since these biomarkers are mechanistically linked in vivo. That the association of retinal venular dilation remains associated with IL-6 but not CRP in the multiple linear regression is consistent with the role of IL-6 role as an inducer of CRP. IP-10 is a marker of type I and type II interferon responses typically induced by bacterial or viral infection, and its association with retinal venous dilation suggests that HIV infection or infections with co-pathogens may contribute to this inflammatory state.[29,30] Elevations of CRP, IL-6, and IP-10 are associated with mortality in persons with HIV infection and AIDS.[29,30,35–40] Elevated IL-6 and CRP levels also predict increased atherosclerosis and an increased risk of incident myocardial infarction in persons with ART-treated HIV infection.[41–44]

Increasing levels of sCD14 and sCD163 are markers of monocyte/macrophage activation, are associated with large-vessel atherosclerosis and inflammation, and are associated with an increased risk of mortality in HIV-infected persons,[30,35–38,42,45,46] but were not associated with retinal vascular caliber in our study. These results suggest that monocyte/macrophage activation may not contribute substantially to retinal vascular changes in persons with AIDS. Elevation of blood I-FABP level is associated with gut epithelial death or turnover, is linked to microbial translocation, and is associated with AIDS dementia and mortality.[30,47]

Elevated KT ratio is a measure of indoleamine 2,3 dioxygenase (IDO) upregulation, which is induced by interfer-

Table 2. Demographics, Comorbidities, HIV Treatment, Virologic, and Immunologic Variables and Retinal Vascular Caliber in Persons With AIDS

		Central Retinal Artery Equivalent			Central Retinal Vein Equivalent		
Variable	**Number**	**Mean, µm**	**SD*, µm**	***P* Value**	**Mean, µm**	**SD, µm**	***P* Value**
Design				0.001			<0.001
AMD	150	151	16		229	23	
No AMD	304	146	17		220	24	
Demographics							
Age, y				<0.001			0.07
<55	356	149	16		224	23	
>55	98	141	17		219	27	
Sex				<0.001			0.05
Male	351	146	16		222	25	
Female	103	153	16		227	21	
Race				<0.001			<0.001
Black	190	151	18		230	23	
White	180	143	15		218	24	
Other	84	148	15		221	22	
Smoking history				0.15			0.001
Never	146	144	16		218	26	
Former	127	148	16		229	23	
Current	102	148	18		222	23	
Missing	79	150	16		226	22	
Comorbidity							
Hypertension				0.01			0.26
Absent	342	149	17		224	24	
Present	112	144	15		221	23	
Diabetes				0.72			0.45
Absent	414	147	17		223	24	
Present	40	147	17		226	24	
Hyperlipidemia				0.12			0.008
Absent	357	148	17		224	24	
Present	97	145	15		218	24	
Cardiovascular disease				0.03			0.28
Absent	319	147	17		223	24	
Present	58	142	16		219	24	
Renal disease				0.09			0.38
Absent	428	148	17		224	24	
Present	26	142	17		219	29	
HIV treatment							
Enrolment				0.05			0.005
On ART	390	147	17		222	25	
Not on ART	64	151	16		231	19	
ART at or prior to enrolment				0.29			0.10
Ever received	423	147	17		223	24	
Never received	31	150	17		230	17	
Virology/immunology							
HIV load (log_{10}(copies/mL))				0.04			0.13
>2.6	260	149	16		225	23	
<2.6	163	146	17		221	25	
CD4+ T cells				0.71			0.79
<200 cells/µL	212	148	17		224	24	
>200 cells/µL	240	147	16		223	24	

ons and other inflammatory mediators, and results in T cell proliferative defects, loss of gut barrier integrity, and neurotoxicity.[30] Elevations of the KT ratio are associated with increased risks of atherosclerosis and mortality in both HIV-infected and HIV-uninfected persons.[30,48–50] Although not associated with CRVE changes, KT ratio was associated with retinal arteriolar narrowing in the simple linear regression, but not the multiple linear regression. Retinal arteriolar narrowing is associated with hypertension and aging in both HIV-infected and HIV-uninfected persons.[18–24]

Caution should be taken in interpreting our results. LSOCA enrolled participants with AIDS and not with earlier stages of HIV infection, so its generalizability to the entire HIV epidemic is uncertain. However, participants enrolled in LSOCA are similar to those with AIDS in the United States,[27] and as such the results should be applicable to patients with AIDS. The data set consisted of 150 participants with AMD matched to 2:1 with age-, sex-, and race/ethnicity-matched controls. The multiple linear regression could only be performed on the subset of participants with results for all 21 candidate variables, resulting in a reduction in the available sample size by approximately one-third. We did not evaluate HIV-uninfected persons. Nevertheless, the inflammatory biomarkers in this study were chosen because they represent immune and

Table 3. Simple Linear Regression of Retinal Vascular Caliber on Plasma Inflammatory Biomarkers in Persons With AIDS

		Central Retinal Artery Equivalent			Central Retinal Vein Equivalent		
Biomarker	**Number**	**Slope***	**95% CI**	***P* Value**	**Slope***	**95% CI**	***P* Value**
CRP	400	1.3	−0.3, 2.9	0.11	3.7	1.4, 6.0	0.002
IL-6	451	0.6	−0.9, 2.1	0.44	3.7	1.6, 5.8	0.001
IP-10	448	0.5	−1.0, 2.0	0.51	2.8	0.6, 5.0	0.01
sCD14	452	−0.3	−1.9, 1.3	0.70	0.8	−1.6, 3.1	0.53
sCD163	454	−0.6	−2.2, 0.9	0.44	1.1	−1.1, 3.3	0.32
KT ratio	429	−2.0	−3.6, −0.4	0.02	−0.9	−3.3, 1.5	0.45
I-FABP	450	−0.6	−2.1, 0.9	0.44	−1.1	−3.3, 1.2	0.34

* Slope in μm/standardized unit. Standardized unit: standard deviation $\log_{10}$(plasma biomarker level).

inflammatory pathways operative in both HIV-infected persons and in HIV-uninfected elderly. The persistent inflammatory state in ART-treated, immunorestored, HIV-infected persons and its overlap with the phenomenon of immunosenescence in HIV-uninfected older persons suggests that associations with systemic inflammation may be easier to detect in populations such as LSOCA than in the general population. The relevance of LSOCA inferences to aging is strengthened by our results demonstrating that participants in LSOCA have retinal vascular calibers comparable to HIV-uninfected persons at least 10 years older.[18] Lastly, because only the systemic compartment (plasma) could be sampled, we cannot ascertain the role, if any, of locally-produced (i.e. intraocular) inflammatory mediators on retinal vascular caliber. Nevertheless, these data suggest a potential role for systemic inflammation in retinal vascular caliber, which may be relevant to both HIV-infected and HIV-uninfected persons.

In conclusion, our data demonstrate that retinal arteriolar and venular dilation in patients with AIDS is associated with AMD and with Black race. Age and cardiovascular disease are associated with retinal arteriolar narrowing, and hyperlipidemia with retinal venular narrowing. Elevation of plasma levels of the inflammatory biomarker IL-6, a marker of innate immune system activation and systemic inflammation, is associated

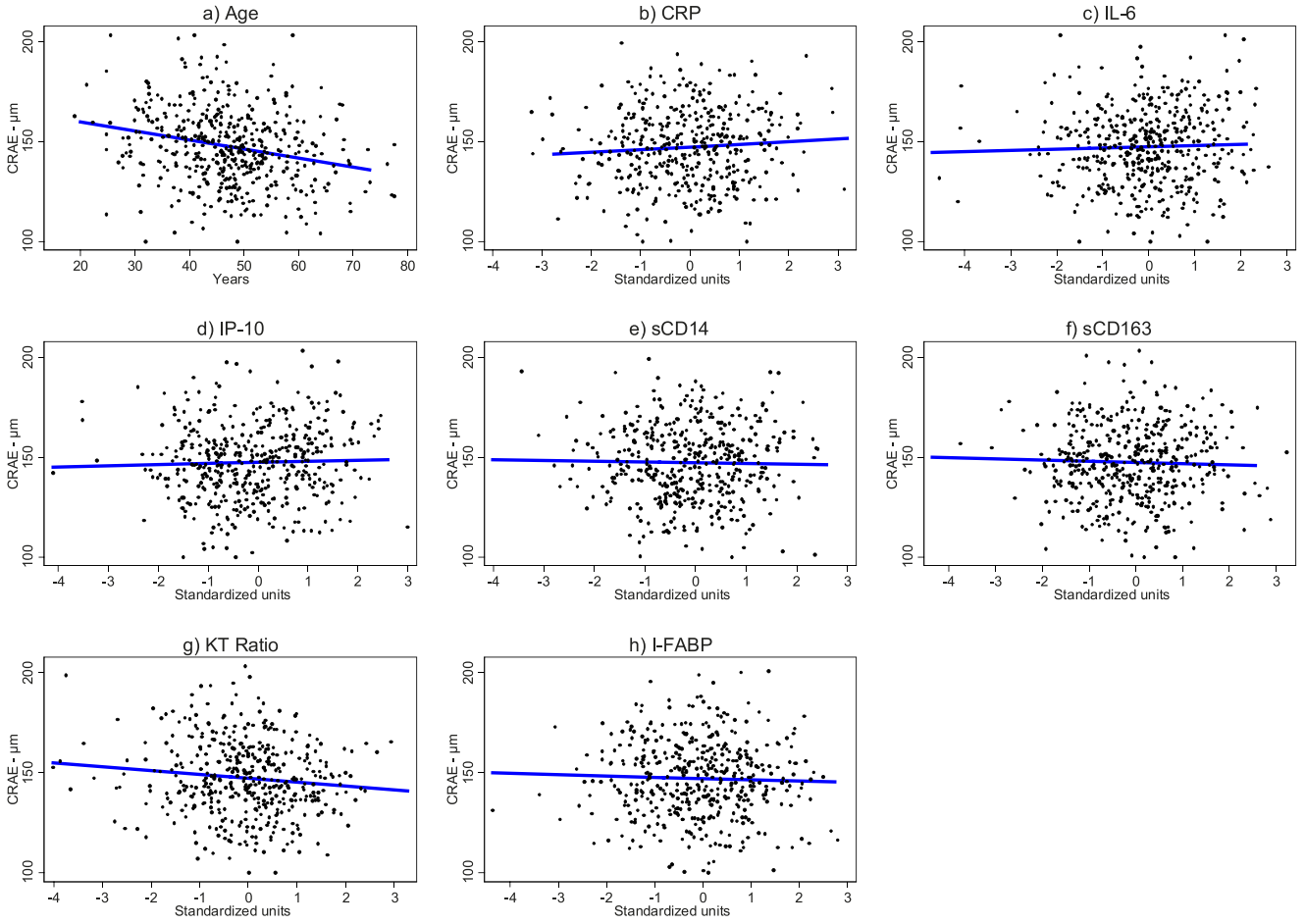

Figure 1. Linear regression of central retinal artery equivalent (CRAE) on (**a**) age, (**b**) CRP, (**c**) IL-6, (**d**) IP-10, (**e**) sCD14, (**f**) soluble CD163 (sCD163), (**g**) KT ratio, (**h**) I-FABP.

Investigative Ophthalmology & Visual Science

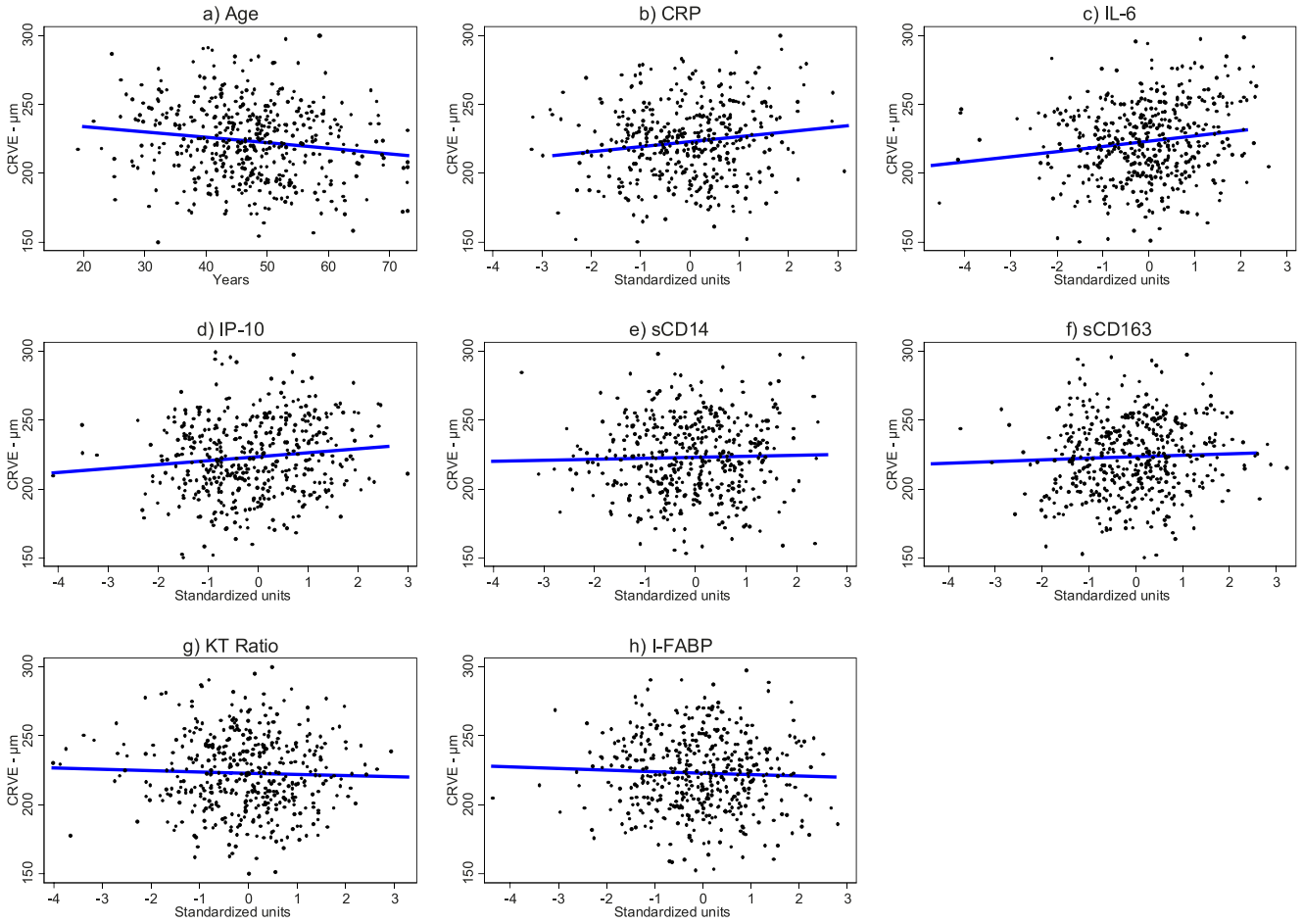

Figure 2. Linear regression of CRVE on (**a**) age, (**b**) CRP, (**c**) IL-6, (**d**) IP-10, (**e**) sCD14, (**f**) sCD163, (**g**) KT ratio; (**h**) I-FABP.

with retinal venular dilation. The simple linear regression suggested an association with CRP and IP-10, also markers of innate immune system activation and systemic inflammation. The multiple linear regression without AMD in the model suggested a possible association of plasma IL-6 with retinal arteriolar dilation as well. Collectively, these results underscore a link between chronic inflammation and vascular disease in ART-treated HIV-infected persons,[41,42,46,50] and the common features of accentuated aging in HIV-infected persons and immunosenescence in the HIV-uninfected elderly suggest a similar relationship may be present in HIV-uninfected persons as well.

Table 4. Multiple Linear Regression* of Retinal Vascular Caliber in Persons with AIDS

	Central Retinal Artery Equivalent			Central Retinal Vein Equivalent		
Categorical Variables	**Mean Δ**	**95% CI**	***P* Value**	**Mean Δ†**	**95% CI**	***P* Value**
AMD (yes vs. no)	9.1	5.2, 12.9	<0.001	10.9	5.3, 16.6	<0.001
Race			<0.001			<0.001
Black vs. white	9.7	5.6, 13.8		12.4	6.4, 18.4	
Black vs. other	1.7	−3.1, 6.5		6.5	−0.5, 13.5	
Sex, male vs. female	−3.6	−8.2, 0.9	0.12	−0.8	−7.2, 5.7	0.82
Hyperlipidemia				−7.5	−13.7, −1.2	0.02
Cardiovascular disease	−5.2	−10.3, −0.1	0.05			
Continuous Variables	**Slope**	**95% CI**	***P* Value**	**Slope**	**95% CI**	***P* Value**
Age, y	−0.26	−0.46, −0.06	0.009	−0.25	−0.53, 0.03	0.08
IL-6, standardized unit‡				5.3	2.7, 8.0	<0.001

* Based on forward selection with $P = 0.05$ for entry using 18 candidate variables and forcing age, race, and sex into the model (see text) among 297 participants with complete data.

† Mean Δ = mean difference for categorical variables. Slope = slope of the regression line for continuous variables.

‡ Standardized unit = standard deviation $\log_{10}$(plasma biomarker level).

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