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Association of Skin Intrinsic Fluorescence with Retinal Microvascular Complications of Long Term Type 1 Diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy

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Abstract

Objective—To determine the association between skin intrinsic fluorescence (SIF), a noninvasive measure of advanced glycation endproducts and oxidative stress in skin, and retinal microvascular complications of long duration type 1 diabetes, proliferative diabetic retinopathy (PDR) and macular edema.

Research Design and Methods—A cross-sectional cohort study of persons with type 1 diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) who participated in a 32-year follow-up examination in 2012–2014. Subjects underwent physical examination, answered a health questionnaire, and had fundus photographs taken. SIF was measured on the underside of the left forearm near the elbow with the SCOUT DS[®] skin fluorescence spectrometer. Two representative SIF measures were used for these analyses: SIF01 excited by an LED centered at 375 nm with correction factors $K_x=0.6$ and $K_m=0.2$ and SIF15 excited by an LED centered at 456 nm with correction factors $K_x=0.4$ and $K_m=0.9$.

Results—The 414 participants had mean diabetes duration of 42.2 years (standard deviation 6.8 years, range 32.9–67.9 years). PDR was statistically significantly associated ($p<.05$) with both SIF measures in multivariate models including other relevant factors (odds ratio [OR] = 1.17 for SIF01 and 1.20 for SIF15).

Conclusion—Skin intrinsic fluorescence measures are independently associated with PDR in the WESDR. Incidence information is needed to evaluate whether there is a causal relationship.

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Keywords

advanced glycation endproducts; macular edema; nephropathy; proliferative diabetic retinopathy; skin intrinsic fluorescence

Light from skin fluorescence in the visible portion of the spectrum can be used to measure the cumulative effects of glycosylation, oxidation and metabolism on the epidermal and dermal layers of the skin, and has been shown to be associated with micro and macrovascular complications of diabetes.^{1–6} Studies comparing skin fluorescence to punch biopsies of human and porcine skin have demonstrated a significant correlation with accumulation of advanced glycation end products (AGEs) such as pentosidine and carboxymethyl lysine, a non-fluorescent adduct.^{7–9}

Advanced glycation endproducts are protein complexes formed by the reaction of reducing sugars with free amino groups on proteins, amino acids or lipids. Skin AGEs known to fluoresce in the visible spectrum include pentosidine, crosslines and pyrropyridine¹. In addition, fluorescence from flavin adenine dinucleotide (FAD), an indicator of oxidative stress, and nicotinamide adenine dinucleotide hydride (NADH), an indicator of cell metabolism, contribute to the cumulative fluorescence signal depending on the wavelength of excitation light used to stimulate skin fluorescence.¹⁰

The Pittsburgh Epidemiology of Diabetes Complications study recently found skin intrinsic fluorescence (SIF) to be cross-sectionally associated with sensory and autonomic neuropathy, microalbuminuria, macroalbuminuria, coronary artery calcification and coronary artery disease in persons with type 1 diabetes^{2–4}. Others have found these measures to be associated with tendon changes in persons with diabetes⁵ and changes in the cardiac tissue of patients undergoing coronary artery bypass surgery.¹¹ Additionally, SIF is a reflection of age, mean glycated hemoglobin A1c (A1c) level, smoking habits and the presence of kidney damage in those with type 1 diabetes.¹² Newly emerging epidemiological data have also shown SIF to be associated with diabetic retinopathy. In subjects with long-term type 1 diabetes in the Pittsburgh Epidemiology of Diabetes Complications Study, a statistically significant ($p < 0.0001$) linear trend between skin fluorescence and progression of diabetic retinopathy was observed.⁴ In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study⁶, SIF was found to be associated with the presence of proliferative diabetic retinopathy (PDR; odds ratio [OR] per standard deviation of SIF = 1.27 [95% confidence interval (CI) 1.04–1.56]) after multivariable adjustment for all significant terms, including subject age, mean A1c over the entire DCCT/EDIC interval, smoking, skin tone, clinic latitude and primary prevention vs. secondary intervention cohort. When mean A1c was replaced in the multivariable model by the most recent A1c, the skin fluorescence OR for PDR increased to 1.74 (95% CI 1.45–2.09).

In virtually all studies of persons with diabetes, higher levels of glycemia have been found to be related to the incidence and progression of diabetic retinopathy and other microvascular complications.^{13–19} However, measures of glycemia explain only 10–15% of the variability in incidence of diabetic retinopathy (Klein R, personal communication, October 21, 2004).

Even considering additional risk factors, there is a gap in explaining the risk of these debilitating complications. Skin intrinsic fluorescence reflects ingested as well as internally produced advanced glycosylated endproducts.²⁰ Some of these are likely longer lived than glycosylated hemoglobin. We had the opportunity to examine whether SIF, a novel biomarker, materially adds to understanding the risk of PDR and macular edema (ME) in a well-defined cohort of persons with long-standing type 1 diabetes who participated in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).

RESEARCH DESIGN AND METHODS

Subjects

The study group for this investigation consisted of 414 persons from the original cohort with type 1 diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) who participated in the 32-year follow-up examination in 2012-2014.²¹⁻²³

Procedures

The examinations were performed in or near the locality of residence of participants. Informed consent conforming to the tenets of the Declaration of Helsinki was obtained from participants before each examination, and Institutional Review Board approval was obtained from the Human Subjects Committee of the University of Wisconsin-Madison. The study operations were performed in adherence to the Health Insurance Portability and Accountability Act.

Measurements

The study evaluations were conducted by trained examiners. The pertinent parts of the ocular and physical examinations for this investigation included measuring blood pressure, dilating the pupils and taking stereoscopic color fundus photographs of 7 standard fields.²⁴⁻²⁶ Participant medical history was obtained for the past year, including a history of kidney or pancreas transplant, whether the subjects smoked (never, past, current) and the medications they used. An aliquot of whole blood was used for determining A1c level, measured by affinity chromatography (Isolab, Inc., Akron, OH), and serum fibrinogen, measured by the Clauss clotting method (Diagnostica Stago, Parsippany, NJ 07054). Urine protein was assessed by dipstick. For each eye, the maximum grade of diabetic retinopathy in any of the 7 standard photographic fields was determined for each of the lesions using the Early Treatment Diabetic Retinopathy Study (ETDRS) classification scheme.²⁷

The SCOUT DS[®] skin fluorescence spectrometer (VeraLight, Inc., Albuquerque, NM) was used to measure skin pigmentation and SIF from the underside of the left forearm near the elbow. Skin fluorescence was excited with light emitting diodes (LEDs) centered at 375, 405, 416, 435 and 456 nm with the resulting emission measured over the 435 to 655 nm spectral range. A white LED was used to measure skin reflectance over the 435 to 655 nm spectral range.

The intrinsic fluorescence correction utilizes the measured skin reflectance at both the excitation wavelengths and the emission wavelengths to mathematically adjust the measured

fluorescence for optical distortion due to absorption of light from melanin and hemoglobin as well as light scattering.^{6,7,12,28} As shown in equation (1), the measured fluorescence (F_{xm}) is divided by reflectance from both the excitation LED (R_x) and the white LED (R_m), which are further scaled by dimensionless exponents k_x and k_m to yield the intrinsic fluorescence (f_{xm}).

$$f_{xm} = \frac{F_{xm}}{R_x^{k_x} R_m^{k_m}} \quad \text{Equation 1}$$

For each of the five excitation LEDs, three different adjustment exponent pairs (k_x , k_m) were used, resulting in 15 SIF measurements for each person. For all of our analyses, we selected two of the SIF measurements, both of which were examined previously in genetic association studies of SIF in the DCCT/EDIC²⁹ and represent the lowest and highest LED excitation wavelengths from this study. SIF01 is a measure of fluorescent AGEs, NADH and FAD excited by the 375 nm LED with adjustment exponents of $k_x=0.6$ and $k_m=0.2$. SIF15 is a measure of AGEs and FAD excited by the 456 nm LED with $k_x=0.4$ and $k_m=0.9$. We explored the relationship of the other SIF measures to the outcomes. Results for them was not materially different from two we include in the current report. To account for variations in skin native pigmentation, which attenuates the detected fluorescence signal, the fluorescence intensity is normalized with the diffuse reflectance signal of the same skin site at the corresponding wavelength. Skin fluorescence was excited with light emitting diodes centered at 375, 405, 416, 435 and 456 nm, with emission measured at 435 and 655 nm spectral range.

Duplicate SIF measures were obtained from each study subject, with the mean of the measurements used for analysis. The intra-subject Hoorn coefficients of variation³⁰ for the duplicate measures were 5.4% for SIF01 and 6.2% for SIF15. SIF values are log normally distributed, so the raw SIF values were logarithmically transformed for statistical analyses. Values for 2 participants were excluded from further analysis because they had skin pigmentation values <50, an indication that their readings on the SCOUT may not have been accurate.

Definitions

Age was defined as the participant's age at the time of the current examination. The duration of diabetes was defined as the period between the participant's age at diagnosis and his or her age at the current WESDR examination. Systolic and diastolic blood pressures were defined as the average of two measurements taken with the Dinamap ProCare 300 (GE Healthcare, Waukesha, Wisconsin, USA). Participants were considered to have proteinuria if they had 1+ on dipstick testing (≥ 30 mg/dl) at the time of the study examination. Presence of PDR was defined as having retinopathy of ETDRS severity level ≥ 60 in at least 1 eye irrespective of past panretinal photocoagulation. If there was no evidence of PDR or treatment for it but the eye had been treated for ME with ocular injection, data from that eye was excluded from the PDR analysis. ME was present if a grader identified thickening of the

retina, with or without partial loss of transparency, within one-disc diameter from the center of the fovea, or if there was none but there was evidence of focal photocoagulation, or if there was a history of ocular injection for macular edema.

Statistical Analysis

All outcomes are binary. Logistic regression models were fitted to the data. Duration of diabetes, A1c, systolic blood pressure, fibrinogen, smoking status and sex were considered for every model. Diabetes duration and A1c were forced into every model, regardless of significance. Other factors were included in stepwise fashion using an inclusion and exclusion p -value of <0.05 . The base model without SIF is Model 1 in each table. Next, we added SIF01 and SIF15 separately to each model (hereafter referred to as Model 2 and Model 3, respectively). Additional analyses were performed substituting A1c averaged over the seven WESDR examination phases for A1c from the current exam (data not shown). SAS version 9 (SAS Institute Inc., Cary, North Carolina, USA) was used for all analyses.

RESULTS

Of the 414 persons who participated in the seventh examination phase of the WESDR, there were 310 with SIF measurements. Thirty-eight of these were excluded due to history of dialysis, kidney or pancreas transplant, or lack of data on PDR or ME. Two of the 272 remaining participants were excluded, as noted in Methods above, because their skin pigmentation values indicated that the SCOUT may not have been accurate. Consequently, there were 270 persons with complete data for either the PDR or ME analyses. Selected characteristics for those who provided information for the analyses at the time of the seventh examination (included) and those persons who did not (excluded) are given in Table 1. Those excluded had slightly longer duration of diabetes, lower current and mean A1c, higher SIF01 and SIF15, higher fibrinogen levels, and were more likely to have had PDR, ME and diabetic nephropathy.

For the PDR analysis, 16 additional persons were excluded due to missing data for either PDR, diabetes duration, A1c or fibrinogen, resulting in data for 254 participants. For the ME analysis, 49 of the 270 were excluded due to missing data for either ME, diabetes duration or A1c, resulting in data for 221 participants.

Multivariable analysis was used to model the relationship of characteristics associated with the presence of PDR before considering SIF01 and SIF15 in the analysis (Model 1 in Table 2). In addition to diabetes duration and A1c, fibrinogen was selected. When SIF01 was added to the model, it was statistically significant in its relation to PDR (OR 1.17; 95% CI 1.01-1.34, Model 2 in Table 2). A similar pattern was seen for SIF15 (OR 1.20 95% CI 1.06-1.35, Model 3 in Table 2). The addition of SIF in the models attenuated the association of diabetes duration, A1c and fibrinogen with PDR.

Similar modeling approaches were employed for examining the associations of SIF01 and SIF15 for ME (Table 3) as an outcome. For ME, the OR for SIF01 was 1.04 (95% CI 0.88-1.23) and the OR for SIF15 was 1.09 (95% CI 0.94-1.27). Inclusion of SIF did not have a meaningful effect on the other relationships in these models.

Since proteinuria is strongly associated with the retinal outcomes (ORs of 5.7 for PDR and 4.2 for ME, respectively), we further explored each of the multivariate models with additional adjustment for proteinuria. There was attenuation of the association of SIF01 in the PDR models and of both SIF measures in the ME models rendering these associations non-significant (data not shown). Other analyses were performed to explore the relationships of both retinal outcomes with the mean A1c instead of current A1c. Mean A1c had stronger and more significant associations and SIF had slightly weaker associations with both retinal outcomes (data not shown). Because we do not have long term measures of all associated variables we limit our primary analyses to our cross sectional data.

CONCLUSIONS

We found significant associations of two SIF measures with the presence of PDR in persons with long-term type 1 diabetes. While adjusting for a long-term measure of glycemia, a similar finding was reported from the DCCT/EDIC study.⁶ Like the DCCT, when we used current A1c, the strength of the OR of SIF01 and SIF15 was slightly higher for both PDR and ME (data not shown). This may reflect that current A1c fails to reflect the importance of relatively higher glycemic levels in the past that have had an effect on the prevalence of PDR and ME. The measure of SIF appears to be a relatively better measure of systemic glycation than current A1c. Thus, when long term data about A1c and long term are lacking, current SIF appears to add more substantively when describing the deleterious effects of glycation.

Other limitations of our analyses include the loss to follow-up. As the WESDR cohort was identified more than 30 years ago, the participants at this examination are survivors. Uncontrolled confounding is always of concern despite our attempts to adjust for important covariates. In addition, another limitation is the relative homogenic ethnicity of this population. While this may have led to less variability in our findings, it limits generalizability to a white population. Another technical feature, and possibly a limitation of these analyses, is that ME was graded from color images. To the extent that this technique leads to underestimating the prevalence of this condition, we may have been unable to detect a relationship between the SIF measures and the retinal vascular outcome.

In conclusion, we have found significant associations of two SIF measures, from different excitation wavelengths, with an important microvascular complication in persons with type 1 diabetes. It will be important to assess this in a longitudinal follow-up to understand the temporal associations between SIF and other covariates on PDR and ME.

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Table 1

Comparison of Included and Excluded Participants

Variable	Included (N = 266)			Excluded (N = 148)		
	N	Mean (SD) or N (%) with Condition	N	Mean (SD) or N (%) with Condition	P-value	
SIF01 (unitless)	270	23.89 (5.22)	40	27.49 (7.00)	<.001	
SIF15 (unitless)	270	1.49 (0.36)	40	1.67 (0.51)	0.005	
Age, yrs.	270	55.54 (8.70)	144	56.63 (9.10)	0.23	
Duration, yrs.	270	41.48 (6.36)	144	43.42 (7.54)	0.006	
A1c (current), %	264	7.96 (1.11)	134	7.34 (1.36)	<.001	
A1c (mean), %	270	8.20 (0.93)	144	7.87 (1.07)	0.001	
Systolic blood pressure, mm Hg	270	136.55 (18.57)	79	134.11 (20.01)	0.31	
Fibrinogen, mg/dL	262	348.47 (82.07)	75	379.25 (104.52)	0.007	
PDR	266	110 (41.35%)	126	77 (61.11%)	<.001	
ME	227	53 (23.35%)	98	48 (48.98%)	<.001	
Proteinuria	248	36 (14.52%)	58	19 (32.76%)	0.002	

SIF, skin intrinsic fluorescence; A1c, glycated hemoglobin A1c; PDR, proliferative diabetic retinopathy; ME, macular edema

Table 2

Association of SIF with PDR

Predictors	Model 1 Without SIF		Model 2 With SIF01		Model 3 With SIF15	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Diabetes duration (per 5 years)	1.224 (0.99, 1.51)	0.061	1.14 (0.91, 1.42)	0.26	1.16 (0.93, 1.44)	0.19
A1c (per 1%)	1.38 (1.08, 1.75)	0.01	1.30 (1.01, 1.66)	0.04	1.27 (0.99, 1.63)	0.06
Fibrinogen (per 50 mg/dL)	1.23 (1.03, 1.46)	0.02	1.17 (0.98, 1.39)	0.09	1.18 (0.99, 1.40)	0.07
log(SIF01_1×6m2) (per 0.1)			1.166 (1.01, 1.34)	0.03		
log(SIF15_5×4m9) (per 0.1)					1.20 (1.06, 1.35)	<.004

SIF, skin intrinsic fluorescence; PDR, proliferative diabetic retinopathy; A1c, glycated hemoglobin A1c

Table 3

Association of SIF with ME

Predictors	Model 1 Without SIF		Model 2 With SIF01		Model 3 With SIF15	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Diabetes duration (per 5 years)	0.99 (0.76, 1.30)	0.95	0.97 (0.73, 1.29)	0.83	0.96 (0.73, 1.27)	0.77
A1c (per 1%)	1.89 (1.39, 2.56)	<.001	1.85 (1.36, 2.53)	<.001	1.81 (1.33, 2.48)	<.001
log(SIF01_1×6m2) (per 0.1)			1.04 (0.88, 1.23)	0.62		
log(SIF15_5×4m9) (per 0.1)					1.09 (0.94, 1.27)	0.24

SIF, skin intrinsic fluorescence; ME, macular edema; A1c, glycated hemoglobin A1c