The Association of Skin Intrinsic Fluorescence With Type 1 Diabetes Complications in the DCCT/EDIC Study

OBJECTIVE—To determine whether skin intrinsic fluorescence (SIF) is associated with long-term complications of type 1 diabetes (T1D) and, if so, whether it is independent of chronic glycemic exposure and previous intensive therapy.

RESEARCH DESIGN AND METHODS—We studied 1,185 (92%) of 1,289 active Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) participants from 2010 to 2011. SIF was determined using a fluorescence spectrometer and related cross-sectionally to recently determined measures of retinopathy (stereo fundus photography), cardiac autonomic neuropathy (CAN; R-R interval), confirmed clinical neuropathy, nephropathy (albumin excretion rate [AER]), and coronary artery calcification (CAC).

RESULTS—Overall, moderately strong associations were seen with all complications, before adjustment for mean HbA1c over time, which rendered these associations nonsignificant with the exception of sustained AER >30 mg/24 h and CAC, which were largely unaffected by adjustment. However, when examined within the former DCCT treatment group, associations were generally weaker in the intensive group and nonsignificant after adjustment, while in the conventional group, associations remained significant for CAN, sustained AER >30 mg/24 h, and CAC even after mean HbA1c adjustment.

CONCLUSIONS—SIF is associated with T1D complications in DCCT/EDIC. Much of this association appears to be related to historical glycemic exposure, particularly in the previously intensively treated participants, in whom adjustment for HbA1c eliminates statistical significance.

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monitoring. The intensive and conventional treatment groups maintained median HbA1c levels of ~7.0 and 9.0%, respectively, during the 6.5-year mean DCCT follow-up.

In 1994, after completion of the DCCT, 1,375 subjects (96% of the surviving cohort), 688 from the conventional arm and 687 from the intensive arm, agreed to participate in the EDIC follow-up study, which included annual examinations measuring diabetes complications (22).

For the current SIF complications analyses, all living EDIC subjects who participated in the annual exam during years 16 or 17 of EDIC (2010 to 2011) were eligible for inclusion. Ninety-two percent (1,185) of the 1,289 active EDIC participants had SIF measured.

Clinical measures
Demographic data and health history were self-reported, and a standardized physical examination was performed annually. BMI was measured every 3 months during the DCCT and yearly during the EDIC Study. All laboratory measurements were performed at the DCCT/EDIC Central Biochemistry Laboratory at the University of Minnesota as previously described (21). HbA1c was measured every 3 months during the DCCT and yearly during the EDIC Study (21,22). AER was measured annually during the DCCT and on alternate years during the EDIC study using a timed 4-h urine collection and expressed per 24 h (21,22). Serum lipids were measured using conventional enzymatic methods from fasting samples obtained yearly during DCCT and on alternate years during EDIC. Serum creatinine was measured annually in DCCT/EDIC and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (23,24).

Total glycomic exposure (mean HbA1c) was calculated as: (pre-DCCT: DCCT eligibility HbA1c X duration of diabetes at study baseline) + (DCCT mean HbA1c X years of follow-up in DCCT) + (EDIC mean HbA1c X years of follow-up in EDIC). Glycomic exposure was also examined using each of these time periods separately.

Clinic latitude was determined as a surrogate for potential differences in vitamin D levels due to sun exposure and was incorporated into the data analysis as a categorical variable with EDIC clinics below and above 37° latitude designated as southern (n = 9) and northern clinics (n = 19), respectively (25–28). Smoking status was determined by subject self-report and categorized as never smoked (<100 cigarettes in a subject's lifetime), previous smoker (quit >1 year ago), or current smoker.

SIF measurement
Repeat measurements of SIF were obtained from the skin on the underside of the left forearm near the elbow using the SCOUT DS skin fluorescence spectrometer. SIF was excited with a light-emitting diodes centered at 375, 405, 416, 435, and 456 nm and was detected over the emission range of 435–655 nm. For these analyses, the 375-nm excited fluorescence was used, with kx set to 0.6 and km set to 0.2. The resulting intrinsic fluorescence, f(x,m), was integrated over the 435–655-nm spectral region and multiplied by 1,000 to give the SIF sum. These values of kx and km were previously determined in the Pittsburgh EDC study to be relevant for the 375-nm excited fluorescence, which had the strongest association with diabetes-related complications in the Pittsburgh EDC cohort (19). The intraindividual, same-day variation in SIF was assessed using the method of the Hoorn Study (18). The intraday Hoorn coefficient of variation was 4.2%, and the between-measurement correlation was 0.963.

Definition of complications
The complications of diabetes reported in this article are retinopathy, nephropathy, neuropathy, and CAC. Each participant was categorized according to the presence or absence of each of these complications at his or her most recent clinical assessment.

Retinopathy. Presence or absence of moderate nonproliferative diabetic retinopathy (NPDR) or worse indicated by microaneurysms plus immunoradiometric assay or moderate retinal hemorrhages (Early Therapy Diabetic Retinopathy Study [ETDRS] score of ≥6) between EDIC years 13–16. Subjects who received pan-retinal scatter photocoagulation (laser) therapy in either eye were counted as having the most severe level of retinopathy thereafter. Retinopathy was measured by standardized seven-field fundus photography biannually during DCCT. During EDIC, it was assessed with identical
methods, but in approximately one-quarter of the cohort each year and in the entire cohort at EDIC years 4 and 10. All photographs were graded centrally using the final ETDRS grading scale (29,30) and DCCT methods with the graders masked to DCCT therapy assignment (21,30).

**NEUROPATHY**. Two measures of neuropathy were used. First, the presence or absence of cardiac autonomic neuropathy (CAN) was assessed by measuring sinus arrhythmia (33). Electrocardiographic RR variation was computed as a dimensionless circular mean vector of R-R intervals (33). Abnormal RR variation was defined as <1.15 in testing done in EDIC years 16/17 (33). Secondly, presence or absence of confirmed clinical neuropathy (CCN) was defined as in previous DCCT/EDIC publications (34,35). The data used for this assessment were obtained from nerve conduction tests done in EDIC years 13/14 (35).

CAC was detected with either multislice or electron beam computed tomography, as previously described (36). We defined categories of CAC (present/absent) using thresholds of CAC >0 and CAC >200 Agatston units from testing done in EDIC year 12.

**Statistical analyses**

Characteristics were compared using the Wilcoxon rank sum test to evaluate treatment group differences for ordinal and numeric variables. The contingency \( \chi^2 \) test was used for categorical variables.

SIF was log transformed, and the first SIF measurement per subject was used for all analyses. The association between log SIF and the most recent complication status was modeled using logistic regression adjusting for variables that have been previously shown to be related to SIF and were statistically significant (37). These comprised age, any eGFR <60 mL/min/1.73 m\(^2\) (categorical adjustment to control for retained AGE products as a consequence of renal function impairment), smoking status (never, ever, or current), skin tone, and clinic latitude. Hypertension and lipid concentrations were not related to SIF (37). Further adjustments were made for total glycemic exposure. Odds ratios (ORs) and 95% CIs are presented per 1 SD (0.21) change in log SIF. Interactions between treatment group and log SIF were also assessed.

**RESULTS**—At the time of SIF determination, the population had a mean age of 51.5 years and diabetes duration of 29.8 years (Table 1). As previously reported, the DCCT former intensive therapy group had a lower prevalence of most complications despite current and prior mean HbA\(_{1c}\) being similar between the two groups starting 5 years from the end of the DCCT in 1993, although no difference was seen for end-stage renal disease and CAN. There was no difference in SIF by former treatment group. Compared with the few (\( N = 104 \)) active DCCT/EDIC participants without an SIF measure, the examined population showed no major differences in baseline age (\( P = 0.97 \)) and duration of diabetes (\( P = 0.64 \)). Nonparticipants had a higher mean DCCT/EDIC/pre-DCCT HbA\(_{1c}\) (8.4 ± 1.0 vs. 8.2 ± 0.9; \( P = 0.02 \)).

Table 2 presents the ORs for each complication per 1 SD change in log SIF after adjustment for age, any eGFR <60 mL/min/1.73 m\(^2\), smoking status, skin tone, and clinic latitude with and without adjustment for total glycemic exposure. Data are presented overall and stratified by DCCT treatment group. Overall, a moderately strong positive risk for each complication was seen in the analyses unadjusted for total glycemic exposure, although magnitude varies (ORs range from 1.15 [CAC >200] to 1.87 [sustained AER ≥30]). These associations were a little higher if eGFR was not included as a covariate (e.g., for sustained AER, the OR unadjusted for mean HbA\(_{1c}\) was 2.19 [95% CI 1.79–2.67] compared with 1.87 [1.52–2.31] (Table 2). All of the overall associations were significant except those for CAC >200, for which the prevalence was low (7%). After adjustment for total glycemic exposure, all ORs were markedly reduced, although those for sustained AER ≥30 and CAC >0 remained significant (\( P < 0.05 \)). When analyzed as continuous outcomes, similar significant associations were seen; however, log (and square root) CAC were now significantly associated with SIF.

Subtle differences emerged on stratification by treatment group, although generally, treatment group by log SIF interactions were significant. In the former intensive therapy group, the strength of the glycemic unadjusted associations with CAN, CCN, and sustained AER ≥30 was somewhat lower than seen for the former conventional group. For CAN, the interaction term for treatment group was significant (\( P < 0.05 \)). In contrast, the associations with retinopathy and CAC were similar. When analyzed continuously, all associations between SIF and CAN, sustained AER, and both CAC transformations were significant for both treatment groups, except for CAN and square root CAC in the former intensive group.

The overall effect of adjustment for total glycemic exposure showed a reduction in the ORs to borderline or no significance for the retinopathy, neuropathy, and nephropathy markers except for sustained AER ≥30 (overall and conventional group) and CAN (conventional group), where significance was retained. The interaction term for treatment group remained significant for CAN (\( P < 0.05 \)). The magnitude of the adjustment effect was fairly consistent across treatment groups. However, the relationship between SIF and CAC appeared to be little affected by the HbA\(_{1c}\) adjustment in either group. When examined continuously, similar patterns were seen by former treatment group, although in the intensive group, neither log or square root CAC was significantly associated with log SIF.

We also simultaneously examined the association between glycemia adjusted log SIF and complications by both DCCT primary prevention versus secondary intervention cohort and treatment group (Table 3). In the primary prevention cohort, log SIF associations with the microvascular complications were generally low (and nonsignificant) in the former intensive therapy group and stronger and significant for CAN and sustained AER ≥30 in the conventional group. The treatment group interaction term for CAN remained significant (\( P = 0.04 \)). For CAC, little difference is seen between former treatment groups, and all associations were nonsignificant. In the secondary intervention cohort, for retinopathy, the relative direction of the associations was different (i.e., now stronger in the former intensive group) (OR 1.23 vs. 0.89), though none of these potential group interactions were significant. Furthermore, in the secondary cohort, no ORs were significant for any complication in either treatment group. When analyzed continuously, in the primary prevention cohort, log AER was significantly associated with log SIF in the conventional group. In the secondary intervention cohort, significant associations were seen for log AER in both groups and for CAC in the conventional group.
CONCLUSIONS—These results demonstrate an association of SIF with complications of T1D in the well-characterized DCCT/EDIC cohort. Generally, fairly strong univariate correlations were seen for all microvascular complications included with weaker associations for CAC. However, on adjustment for total glycemic exposure, the microvascular complication associations were totally eliminated in the former intensive therapy group and remained significant only for CAN and sustained AER in the former conventional group. The weaker CAC associations were not further affected by controlling for glycemic exposure. These differences by DCCT treatment group appear complex, but fairly small and significant interactions were found only for CAN. Finally, it should be noted that there is no current difference between the former DCCT intensive and conventional groups in SIF, which was measured 16 to 17 years after the large separation in HbA1c between the groups ended.

SIF is not simply a function of glycemic exposure and AGE formation, but may reflect many other factors, some of which we are able to control, such as skin fluorescence/pigment and hemoglobin levels. Given these multiple determinants, SIF may potentially reflect more than glycemic exposure and AGE formation. However, the current data suggest that any added information is largely linked to
Table 2—Log SIF association with most recent complication status overall and by original DCCT treatment group

| Complications | N (%) | Unadjusted for HbA1c | Adjusted for total glycemic exposure† |
|---------------|-------|-----------------------|---------------------------------------|
|               |       | Overall | Conventional | Intensive | Overall | Conventional | Intensive |
|               |       |         |             |           |         |             |           |
| Categorical outcomes | | | | | | | |
| Moderate NPDR or worse | 436 (37) | 1.44 (1.24–1.66) | 1.41 (1.11–1.79) | 1.10 (0.94–1.30) | 1.08 (0.86–1.34) | 1.15 (0.89–1.49) |
| CAN | 376 (33) | 1.36 (1.16–1.59) | 1.05 (0.84–1.31) | 1.14 (0.96–1.34) | 1.43 (1.13–1.80) | 0.88 (0.69–1.11) |
| CCN | 329 (30) | 1.36 (1.16–1.60) | 1.28 (1.01–1.62) | 1.09 (0.92–1.29) | 1.16 (0.91–1.47) | 1.03 (0.80–1.33) |
| Sustained AER ≥30 | 165 (14) | 1.87 (1.52–2.31) | 1.54 (1.09–2.18) | 1.50 (1.20–1.87) | 1.66 (1.24–2.21) | 1.28 (0.89–1.84) |
| Any CAC | 315 (29) | 1.24 (1.05–1.46) | 1.23 (0.98–1.55) | 1.20 (1.01–1.42) | 1.26 (0.98–1.62) | 1.17 (0.93–1.48) |
| CAC >200 | 78 (7) | 1.15 (0.88–1.52) | 1.17 (0.78–1.76) | 1.16 (0.87–1.54) | 1.16 (0.79–1.72) | 1.19 (0.79–1.81) |

Continuous outcomes

| R-R variation | 1,141 | -9.93 ± 2.77 (0.0003) | -13.80 ± 3.65 (0.0002) | -4.73 ± 4.19 (0.2586) | -2.98 ± 2.74 (0.2766) | -8.29 ± 3.74 (0.0271) | 1.85 ± 4.02 (0.6463) |
| Log AER | 1,172 | 1.37 ± 0.20 (<0.0001) | 1.11 ± 0.26 (<0.0001) | 0.87 ± 0.20 (<0.0001) | 0.91 ± 0.23 (<0.0001) | 1.11 ± 0.26 (0.0040) | 0.96 ± 0.49 (0.0086) |
| Log CAC | 1,069 | 1.07 ± 0.33 (0.0013) | 1.12 ± 0.56 (0.0139) | 0.97 ± 0.49 (0.0476) | 0.99 ± 0.34 (0.0038) | 1.19 ± 0.47 (0.0127) | 0.86 ± 0.50 (0.0860) |
| Square root CAC | 1,069 | 2.75 ± 1.15 (0.0172) | 3.58 ± 1.60 (0.0257) | 1.63 ± 1.67 (0.3273) | 2.63 ± 1.19 (0.0272) | 3.97 ± 1.67 (0.0233) | 1.50 ± 1.70 (0.3781) |

All models are adjusted for age, any eGFR <60 ml/min/1.73 m², smoking status, skin tone, and clinic latitude. †Total mean HbA1c is calculated by summing (DCCT/EDIC eligibility HbA1c duration of diabetes at study baseline), (DCCT mean HbA1c × years of follow-up on DCCT), and (EDIC mean HbA1c × years of follow-up in EDIC) and dividing by total duration of diabetes. ‡Data are ORs (95% CI) per 1 SD (0.21) change in log SIF given all other covariates are held constant. §Data are β coefficients ± SE (P value) representing the expected change in a continuous outcome for a one-unit change in log SIF given all other covariates are held constant.

The observation that intensive and conventional groups agree in terms of SIF is not surprising given the conventional do not currently differ in glycemic control. Firstly, it suggests that intensive treatment still retains some additional, albeit borderline significant, potential new pathways to complications after glycemic exposure is eliminated by controlling for lifetime glycemic exposure. Secondly, because SIF shows significant correlations with mean HbA1c over prior periods up to 15 years (37), it is also likely that the associations are being underestimated as there are inter-patient variations in SIF levels. Further research is necessary to determine whether SIF may be useful in quantifying potential new pathways to complications after glycemic exposure is eliminated by controlling for lifetime glycemic exposure.
value) representing the expected change in a continuous outcome for a one-unit change in log SIF given all other covariates are held constant.

Data are ORs (95% CI) per 1 SD (0.21) change in log SIF given all other covariates.

‡ Data are adjusted for age, any eGFR < 60 mL/min/1.73 m², smoking status, skin tone, clinic latitude, and total glycemic exposure.

Table 3—Log SIF association with most recent complication status by original DCCT cohort assignment and treatment group

| Complication | Conventional (N = 294) | Intensive (N = 294) | Conventional (N = 279) | Intensive (N = 279) |
|--------------|------------------------|---------------------|------------------------|---------------------|
| **OR (95% CI)** | 1.34 (0.87-2.02) | 1.31 (0.87-2.02) | 1.34 (0.87-2.02) | 1.31 (0.87-2.02) |
| **OR (95% CI)** | 0.99 (0.68-1.47) | 0.99 (0.68-1.47) | 0.99 (0.68-1.47) | 0.99 (0.68-1.47) |
| **OR (95% CI)** | 1.17 (0.75-1.80) | 1.17 (0.75-1.80) | 1.17 (0.75-1.80) | 1.17 (0.75-1.80) |
| **OR (95% CI)** | 0.97 (0.61-1.55) | 0.97 (0.61-1.55) | 0.97 (0.61-1.55) | 0.97 (0.61-1.55) |
SIF–CAC association may be stronger in those with more advanced duration and CAC, as seen in EDC.

In terms of neuropathy, EDC also studied both CAN and distal symmetric polyneuropathy and again found strong associations with both measures independent of 18-year mean HbA1c. Indeed, for CAN, the receiver operating characteristic for SIF was 0.8, while for mean HbA1c, it was only 0.57. Similar disparity was seen for distal symmetric polyneuropathy (0.78 vs. 0.59). Our CAN results are thus consistent with these EDC findings and with prior data showing AGE accumulation in neural tissue (39). Though analytic measures are different, it does seem SIF associations are weaker in DCCT/EDIC than in EDC when assessed in terms of incremental association after accounting for historic glycemic control. A major factor beyond the differing duration is the far greater detailed assessment of historic control (HbA1c), both in terms of number of measures and the proportion of diabetes duration covered by HbA1c values. There are a number of strengths and weaknesses in the current analyses. While the large sample size of DCCT/EDIC and the detailed glycemic assessments are great strengths, the relatively mild complication status of the population at present means that there is low representation of advanced stages of complications in which stronger associations may be seen. Another major limitation is the cross-sectional nature of the analysis, particularly as some complications were assessed up to 3 or 4 years earlier than SIF (e.g., CAC), and thus, their status may have changed. Prospective follow-up of this valuable cohort should partially address these concerns.

In conclusion, these analyses have shown moderately strong associations between SIF and a number of markers of diabetes complications in the DCCT/EDIC cohort despite the SIF measures not being determined, in some instances, at the same time as complication assessment. The associations appear weaker in the former intensive therapy group. Though history of glycemic exposure largely eliminates these associations in the former intensive therapy group, they remain significant for CAN and sustained AER in the former conventional group. Prospective studies are, however, needed to fully evaluate the predictive value of SIF for complications. Further investigations to understand the pathophysiologic basis for these associations and the suggestive treatment group differences are also warranted.

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T.J.O. researched the data, wrote significant portions of the manuscript, reviewed, and edited the manuscript, and contributed to the discussion. T.J.L. researched the data, wrote a portion of the manuscript, reviewed, and edited the manuscript, and contributed to the discussion. P.A.C., B.H.B., and J.M. researched the data, reviewed and edited the manuscript, and contributed to the discussion. C.C. and R.A.G.-K. reviewed and edited the manuscript and contributed to the discussion. J.W. and K.A. researched the data. A.B. contributed to the discussion. S.V. reviewed and edited the manuscript. P.A.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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