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

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OBJECTIVES—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 (stereofundus 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.

THE micro- and macrovascular complications of type 1 diabetes (T1D) are thought to result, primarily, from exposure of tissues to high glucose concentrations and to be reduced by intensive glycemic control (1,2). Although the pathogenesis is poorly understood, one mechanism of hyperglycemia-associated tissue damage appears to operate through enhanced formation and accumulation of advanced glycation end products (AGEs) (3,4). AGEs are the stable final products of complex reactions, many involving free radical oxidation, between reducing sugars and free amino groups in proteins. AGE formation is considered a stoichiometric, nonenzymatic process that is enhanced in diabetes not only by elevated glucose concentrations, but also by increased oxidative stress (3,5). AGEs include glucose- or carbohydrate-derived adducts to proteins, and some include cross-links within and between protein molecules.

Numerous studies have focused on AGE modification of skin collagen (6–16) as an accessible, long-lived protein that may reflect cumulative AGE-mediated tissue damage elsewhere. Skin AGE content accumulates on long-lived proteins with advancing chronological age and is accelerated in diabetes (17). In a study of skin biopsy samples collected near the end of the Diabetes Control and Complications Trial (DCCT) (from 1992 to 1993), levels of AGEs in collagen were lower in the intensive treatment group compared with the conventional group (8). Furthermore, in a more recent analysis of the same tissue samples, the initial glycation product (assessed as furosine content) and the AGE carboxymethyllysine were shown to predict the progression of both retinopathy and nephropathy independently of HbA₁c levels (13). As measures requiring skin biopsy are obviously not generally applicable in the clinical setting, a noninvasive, surrogate measure of AGE content reflecting skin collagen might be of great potential value.

Some AGE products fluoresce when excited with near-ultraviolet and blue light, and measures of fluorescence in tissue biopsies, including skin collagen, have been found to correlate with levels of specific AGE products (r = 0.55) (10,11). It is thus possible that skin fluorescence may act as a surrogate marker for AGE content and provide an opportunity for noninvasive measurement of these products (6,8,10,11). It should, however, be recognized that skin fluorescence has multiple determinants beyond AGE and thus may also provide additional information concerning risk for complications. The SCOUT DS instrument noninvasively measures AGE-related, and other, fluorescence in human skin, called skin-intrinsic fluorescence (SIF), controlling for subject-specific light scattering and skin melanin and hemoglobin content (10,11).

Preliminary SIF data from the Pittsburgh Epidemiology of Diabetes Complication...
SIF and complications in the DCCT/EDIC study

RESEARCH DESIGN AND METHODS

Study sample
The inclusion and exclusion criteria for the DCCT and the treatment protocol have been described in detail (21). Briefly, 1,441 subjects with T1D between 13 and 39 years of age were recruited into the DCCT between 1983 and 1989; 53% were male. The primary prevention cohort consisted of 726 subjects who, at study baseline, had no retinopathy, a urinary albumin excretion rate (AER) <40 mg/24 h, and diabetes duration of 1–5 years. The secondary intervention cohort consisted of 715 subjects who had very mild to moderate nonproliferative retinopathy, urinary AER ≤200 mg/24 h, and diabetes duration of 1–15 years. As part of the screening for the DCCT, individuals were excluded if they had hypertension, a history of symptomatic ischemic heart disease, the presence of major electrocardiogram abnormalities, or severe hypercholesterolemia. Subjects were randomly assigned to either intensive (n = 711) or conventional (n = 730) treatment arms and assessed for complications at frequent follow-up visits. Intensive therapy included either multiple (at least three) daily insulin injections or continuous subcutaneous insulin infusion with external insulin pumps, with the goal of achieving glycemic control as close to the nondiabetic range as safely possible; specifically, HbA1c <6.05% guided by frequent daily self-blood glucose 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 the DCCT and on alternate years during the EDIC Study. 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 glycemic exposure (mean HbA1c) was calculated as: (pre-DCCT: DCCT eligibility HbA1c × duration of diabetes at study baseline) + (DCCT mean HbA1c × years of follow-up in DCCT) + (EDIC mean HbA1c × years of follow-up in EDIC). Glycemic 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, f375, was integrated over the 435–655-nm spectral region and multiplied by 1,000 to give the SIF sum. These values of k375 and k435 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 intrasubject, 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 paper 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
and 15/16) (31,32). Consecutive visits at EDIC years 13/14
arrhythmia (33). Electrocardiographic
(CAN) was assessed by measuring sinus
R
and log SIF were also assessed. Odds ratios (ORs) and 95% CIs are pre-
were made for total glycemic exposure. Further adjustments
status was modeled using logistic regres-
sion adjusting for variables that have been
interaction term for treatment group
was different (i.e., now stronger in the
former intensive group) (OR 1.23 vs.
0 remained significant. In the second-
ary intervention cohort, log SIF associations with the
microvascular complications were generally
low (and nonsignificant) in the for-
mer 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 associa-
tions were nonsignificant. In the sec-
ondary 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. Fur-
thermore, 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 in-
tervention cohort, significant associations
were seen for log AER in both groups and
for CAC in the conventional group.

RESULTS—At the time of SIF determina-
tion, 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 complica-
tions despite current and prior mean
HbA1c being similar between the two
groups starting 5 years from the end of
the DCCT in 1993, although no differ-
ence is seen for end-stage renal disease
and CAC. There was no difference in
SIF by former treatment group. Com-
pared 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 HbA1c
(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 m², smoking status, skin
tone, and clinic latitude with and without
adjustment for the 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 un-
adjusted for total glycemic exposure, al-
though magnitude varies (ORs range
from 1.15 [CAC ≥200] to 1.87 [sustained
AER ≥30]) of the glycemic unadjusted associations
were somewhat lower than seen for the
former conventional group. In the secondary prevention group,
all associations between SIF and
were similar. When analyzed continu-
ously, 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 reduc-
tion in the ORs to borderline or no signifi-
cance for the retinopathy, neurop-
athy, and nephropathy markers except for
sustained AER ≥30 (overall and conven-
tional 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 be-
tween SIF and CAC appeared to be little
affected by the HbA1c adjustment in ei-
ther group. When examined continu-
ously, 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 second-
ary intervention cohort and treatment
group (Table 3). In the primary preven-
tion cohort, log SIF associations with the
microvascular complications were gen-
erally low (and nonsignificant) in the for-
mor 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
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When analyzed continuously, in the
primary prevention cohort, log AER was
significantly associated with log SIF in the
conventional group. In the secondary in-
tervention 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

| Complication | N (%) | Unadjusted for HbA1c | | | | | Adjusted for total glycemic exposure† |
|---------------|-------|----------------------|--|---|---|---|---|---|---|
|               |       | Overall              | Conventional | Intensive | Overall | Conventional | Intensive |
|               |       | ORs (95% CI)‡        | ORs (95% CI)‡ | ORs (95% CI)‡ | ORs (95% CI)‡ | ORs (95% CI)‡ | ORs (95% CI)‡ |
| Categorical outcomes |       |                      |               |               |                      |               |               |
| Moderate NPDR or worse | 436 (37) | 1.44 (1.24–1.66) | 1.44 (1.18–1.77) | 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) | 1.68 (1.34–2.09) | 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) | 1.42 (1.14–1.78) | 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) | 2.06 (1.57–2.72) | 1.54 (1.09–2.18) | 1.50 (1.20–1.87) | 1.66 (1.24–2.11) | 1.28 (0.89–1.84) |
| Any CAC        | 315 (29) | 1.24 (1.05–1.46) | 1.25 (0.98–1.59) | 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) | 1.13 (0.77–1.66) | 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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>R-R variation</th>
<th>Log AER</th>
<th>Log CAC</th>
<th>Square root CAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>β coefficient ± SE (P value)</td>
<td></td>
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<tr>
<td></td>
<td>1,141</td>
<td>−9.93 ± 2.77 (0.0003)</td>
<td>−13.80 ± 3.65 (0.0002)</td>
<td>−4.73 ± 2.74 (0.2586)</td>
<td>−2.98 ± 2.74 (0.2766)</td>
</tr>
<tr>
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<td>1,172</td>
<td>1.37 ± 0.20 (&lt;0.0001)</td>
<td>1.61 ± 0.31 (&lt;0.0001)</td>
<td>1.11 ± 0.26 (&lt;0.0001)</td>
<td>0.87 ± 0.02 (&lt;0.0001)</td>
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<td>1,069</td>
<td>1.07 ± 0.33 (0.0013)</td>
<td>1.12 ± 0.56 (0.0139)</td>
<td>0.97 ± 0.49 (0.0476)</td>
<td>0.99 ± 0.34 (0.0038)</td>
</tr>
<tr>
<td></td>
<td>1,069</td>
<td>2.75 ± 1.15 (0.0172)</td>
<td>3.58 ± 1.60 (0.0257)</td>
<td>1.63 ± 1.67 (0.3273)</td>
<td>2.63 ± 1.19 (0.0272)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Complication</th>
<th>Primary prevention cohort</th>
<th>Secondary intervention cohort</th>
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<tbody>
<tr>
<td></td>
<td>Conventional (N = 294)</td>
<td>Intensive (N = 298)</td>
</tr>
<tr>
<td></td>
<td>ORs (95% CI)‡</td>
<td>ORs (95% CI)‡</td>
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<tr>
<td>Categorical outcomes</td>
<td></td>
<td></td>
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<tr>
<td>Moderate NPDR or worse</td>
<td>1.28 (0.92–1.77)</td>
<td>0.93 (0.60–1.44)</td>
</tr>
<tr>
<td>CAN</td>
<td>1.53 (1.07–2.18)</td>
<td>0.74 (0.51–1.08)</td>
</tr>
<tr>
<td>CCN</td>
<td>1.14 (0.79–1.63)</td>
<td>1.01 (0.66–1.53)</td>
</tr>
<tr>
<td>Sustained AER ≥ 30</td>
<td>2.45 (1.51–3.96)</td>
<td>1.10 (0.60–2.00)</td>
</tr>
<tr>
<td>Any CAC</td>
<td>1.21 (0.83–1.75)</td>
<td>1.18 (0.82–1.71)</td>
</tr>
<tr>
<td>CAC &gt; 200</td>
<td>1.00 (0.54–1.85)</td>
<td>0.79 (0.36–1.71)</td>
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<tr>
<td>Secondary intervention cohort</td>
<td></td>
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<tr>
<td></td>
<td>Conventional (N = 279)</td>
<td>Intensive (N = 314)</td>
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<tr>
<td></td>
<td>ORs (95% CI)‡</td>
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‡ Data are ORs (95% CI) per 1 SD (0.21) change in log SIF given all other covariates are held constant.

Continuous outcomes

| R-R variation                  | −5.72 ± 5.68 (0.3145) | 5.97 ± 6.06 (0.3249) |
| Log AER                        | 0.95 ± 0.44 (0.0300)  | 0.54 ± 0.34 (0.1113) |
| Log CAC                        | 0.70 ± 0.62 (0.2635)  | 0.77 ± 0.58 (0.1867) |
| Square root CAC                | 2.07 ± 2.05 (0.3153)  | 0.64 ± 1.63 (0.6960) |

| R-R variation                  | −8.53 ± 4.85 (0.0798) | −1.03 ± 5.53 (0.8521) |
| Log AER                        | 1.11 ± 0.44 (0.0133)  | 0.88 ± 0.38 (0.0230)  |
| Log CAC                        | 1.77 ± 0.73 (0.0167)  | 0.73 ± 0.81 (0.3725)  |
| Square root CAC                | 5.55 ± 2.68 (0.0394)  | 1.61 ± 2.99 (0.5916)  |

All models are adjusted for age, any eGFR < 60 mL/min/1.73 m², smoking status, skin tone, clinic latitude, and total glycemic exposure. ‡ 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 ± SEs (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.
Further investigations to understand the predictive value of SIF for complications. CAN and sustained AER in the former these EDC polyneuropathy (0.78 vs. 0.59). Our disparity was seen for distal symmetric pendent of 18-year mean HbA1c. I n - associations with both measures inde- pendants of glycemic exposure largely eliminates 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 inde- pendent of glycemic exposure largely eliminates 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 inde- pendent of 18-year mean HbA1c. In - associations with both measures inde- pendants of glycemic exposure largely eliminates those with more advanced duration and CAC, as seen in EDC.

Pathophysiologic basis for these associa- tions and the suggestive treatment group differences are also warranted.

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T.J.O. researched the data, wrote signifi- cant 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. re- searched 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.

Parts of this study were presented in abstract form at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

References


