Association of Skin Intrinsic Fluorescence with Cumulative Glycemic Exposure in the DCCT/EDIC Study

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Background

- DCCT/EDIC has shown that glycemic exposure (i.e. overall mean A1c) is strongly associated with microvascular complications
- DCCT/EDIC previously showed that in skin collagen, obtained by biopsy, advanced glycation endproducts (AGEs) are independently associated with retinopathy and nephropathy in type 1 diabetes[1,2]
- AGE formation is driven by cumulative glycemic exposure, oxidative stress and, possibly, individual subject genetics
- Skin intrinsic fluorescence (SIF), which can be measured noninvasively, has been shown to correlate with AGE accumulation[3]
- DCCT/EDIC represents a unique study in which to examine the association of SIF with glycemic exposure

Methods

Glycemic Exposure

- A1c was measured at eligibility visit and quarterly during the DCCT
- A1c is measured annually in EDIC (1994 onwards)

Significant Adjustment Variables

- Subject age in years
- Smoking status categorized as never (less than 100 cigarettes in lifetime), previous (quit more than a year ago) and current
- Clinic latitude expressed as a categorical variable for clinics above 37° latitude (potential difference in endogenous vitamin D)
- Skin tone expressed as the sum of the skin reflectance over the 435 to 655 nm region (Δs in melanin, hemoglobin and light scattering)
- Albumin excretion rate (AER) is weighted mean from DCCT+EDIC

SIF Measurement

- Noninvasive assessment of SIF was performed using an investigational skin fluorescence device (SCOUT)
  - Left volar forearm illuminated with 375 nm and white light
  - SIF computed via the intrinsic correction formula[3], K_x=0.6, K_m=0.2

- SIF measured on 1,175 of 1,354 (87%) living participants at all 28 clinics (1 device per clinic) during years 16 to 18 of the EDIC study
  - 2 measurements (same day) per subject, CV = 4.3%, R^2=0.927
  - 7% of the log (SIF) variance is due to measurement imprecision
  - DCCT intensive (INT) and conventional (CONV) therapy cohorts

Statistical Methods

- Natural log-transformed SIF to produce normal distribution
- Total glycemic exposure computed by summing DCCT/EDIC eligibility A1c x duration of diabetes at study baseline, DCCT mean A1c x years of follow-up in DCCT and EDIC mean A1c x years of follow-up in EDIC
- First SIF measurement per subject used for all analyses
- Examined following variables and kept those significant at $p < 0.05$
  - Subject age, duration of diabetes, triglycerides, AER, eGFR, smoking, diastolic BP, systolic BP, skin tone, BMI, clinic latitude, use of antihypertensive meds ever, use of statins ever
- Correlations are adjusted for significant effects of subject age, smoking status, skin tone, clinic latitude, AER and glycemic exposure
  - Reported as the proportion of variation (R^2) in log (SIF) explained by mean A1c over various time periods

Results

Table 1. Characteristics of study participants

Characteristic	SCOUT Cohort (N=1,175)
Age (years)	51.5 ± 6.9
Male gender	615 (53)
Primary prevention cohort assignment	569 (49)
Current smoker	135 (12)
Subjects from Clinic latitude > 37° N	843 (73)
Duration of Diabetes (years)	29.8 ± 4.9
Triglycerides (mg/dl) *	85.0 ± 42.6
AER (mg/24 hrs) *	47.2 ± 155.3
eGFR (mL/min/1.73 m^2) *	108.4 ± 11.7
Systolic blood pressure (mm Hg) *	118.7 ± 8.3
Diastolic blood pressure (mm Hg) *	74.3 ± 5.2
Measure of skin tone (arbitrary units)	257.7 ± 47.9
Body mass index (kg/m^2)	28.7 ± 5.4
Most recent HbA1c (%)	7.9 ± 1.3
Total glycemic exposure (%)	8.2 ± 0.9
*Data are N (%) or Mean ± SD. * DCCT/EDIC weighted mean*	

Table 2. Unadjusted Correlation (R^2) with log(SIF)

Glycemic Exposure	EDIC last 5 yrs	EDIC last 10 yrs	EDIC all yrs	DCCT only	DCCT + EDIC	Pre + DCCT + EDIC
Treatment + Gender (N)						
INT + Male (315)	0.033	0.036	0.052	0.008	0.042	0.058
INT + Female (292)	0.020	0.037	0.051	0.004	0.039	0.048
CONV + Male (306)	0.038	0.056	0.079	0.070	0.095	0.097
CONV + Female (262)	0.059	0.064	0.073	0.006	0.070	0.089
All Subjects (1,175)	0.035	0.046	0.062	0.011	0.057	0.069

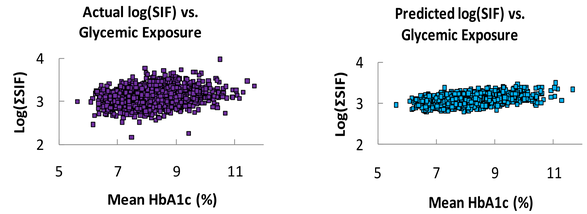
- Correlation between log (SIF) and varying lengths of glycemic exposure are highly significant ($p < 0.0001$) with exception of the DCCT only period ($p<0.03$)
- Correlation increases somewhat with longer glycemic exposure
- Correlations larger in conventional vs intensive treatment group
- When compared to all other glycemic exposure periods, the DCCT only period has reduced correlation of glycemic exposure with log (SIF) in the intensive therapy cohort and conventional therapy females

Table 3. Adjusted Correlation (R^2) with log(SIF)

	Treatment Group and Gender				
	All Subjects	INT+Male	INT+Female	CONV+Male	CONV+Female
Pre+DCCT+EDIC Mean A1c	0.035	0.028	0.022	0.055	0.035
Age	0.174	0.186	0.202	0.203	0.096
AER	0.009	0.013	*0.002 (NS)*	*0.004 (NS)*	0.018
Smoking status	0.050	0.050	0.032	0.037	0.033
Skin tone	0.039	0.044	0.078	0.027	0.020
Clinic Latitude	0.019	0.025	0.010	0.019	0.025
R^2	0.329	0.380	0.345	0.350	0.231

- All model terms are significant except ones followed by (NS)
- The model R^2 for the INT+Male, INT+Female and CONV+Male groups are not significantly different from each other
- The reduction in model R^2 in the CONV+Female group is marginally significantly lower ($p \leq 0.070$) and driven by a reduced age correlation
- Chronological age is the most important term in all adjusted models
- The All Subjects model explains 33% of the log (SIF) variance

Figure 1. Scattergrams of log(SIF) & Glycemic Exposure



- The fully adjusted models explain significantly more SIF variance than glycemic exposure alone ($p < 0.0001$)
- The log (SIF) variance not explained by the fully adjusted model and measurement imprecision may be due to a combination of individual patient genetics, noise from fluorophores that are sensitive to short term metabolic fluctuations (e.g. NADH), imperfect correction for patient specific skin characteristics, residual instrument bias and inaccuracies in the model variables

Conclusions

Over the 23.5 years of DCCT/EDIC, a model comprised of glycemic exposure as represented by the overall mean HbA_{1c} along with subject age, smoking status, skin tone, clinic latitude and AER explained the most skin intrinsic fluorescence variance in both the combined and stratified analyses. In addition, intriguing differences in the log (SIF) association with "DCCT only" glycemic exposure were found by treatment group and gender which warrant further study.

It is known that glycemic exposure, age, smoking and AER are all significantly associated with the vascular complications of diabetes. As SIF partially reflects the influence of these factors, it may serve as a marker of diabetes complications risk.[4]

References

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