Skin Fluorescence and Type 1 Diabetes Complications: A New Marker of Complication Risk

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Background

Advanced glycation end products (AGEs) are macroprotein complexes formed by the Maillard reaction of reducing sugars with free amino groups on proteins, amino acids, or lipids.
Although they increase naturally with age, their formation is accelerated with chronic hyperglycemia and oxidative stress. AGEs are associated with almost all long-term complications of diabetes, and increased levels have been observed in the collagen of those with diabetes. In the Diabetes Control and Complications Trial, AGEs were a better marker of progression to micro-vascular complications than was A1C (Monnier et al, 1999). Several AGEs form fluorescent molecular cross-links. Increased fluorescence has been observed in the skin, retina, and kidney of individuals with diabetes (Forbes et al, 2005). Conventional AGE assays require a skin biopsy and are time intensive. Skin fluorescence provides a summary measure of skin AGEs and may be a strong indicator of diabetes complications.

Purpose

To evaluate the efficacy of an investigational non-invasive skin fluorescence measurement in identifying subjects with type 1 diabetes complications and to compare the non-invasive technique to traditional measures of chronic glycemic exposure.

Study population
- Pittsburgh Epidemiology of Diabetes Complications Study sub cohort (n=47)
- Childhood onset (age < 17 years) type 1 diabetes (diagnosed between 1950-1980)
- Study baseline: 1986-1988, biennial assessment thereafter
- Skin fluorescence assessment period: June-December, 2007

Methods

Subjects place their volar forearm on the instrument's cradle. The instrument illuminates the skin with near-ultraviolet and blue light. The resulting skin reflectance and fluorescence are collected and quantified by the instrument.

Fluorescence was excited with a 375nm LED and detected over the 400-660 nm emission window. The intrinsic dermal fluorescence (IF) is computed using both skin fluorescence and reflectance measurements. The IF correction removes spectral distortion due to melanin, hemoglobin and light scattering. The intrinsic fluorescence was age-corrected to adjust for the accumulation of skin AGEs in normal health

Statistical Analyses

A1 months was calculated by multiplying the number of A1C units above normal at each exam period by the number of months between the midpoints of the preceding and succeeding exam intervals. Updated mean A1C was calculated by taking the average A1C during the 18 years of follow-up.

Pearson's correlations were used to determine the association of skin fluorescence with renal function and coronary artery calcification. Logistic regression analysis was used to determine the association of skin fluorescence, A1 months, and mean A1C with chronic complications of type 1 diabetes. Receiver operator characteristic (ROC) curves and Akaike's Information Criterion (AIC, lower is better) were used to compare the ability of skin fluorescence and long term glycemic control (A1 months and updated mean A1C) in detecting chronic complications of type 1 diabetes.

Results

Table 1: Baseline characteristics of the 47 subjects studied, mean (std) or %.

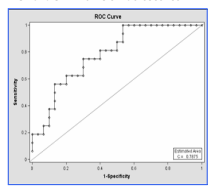
Age (years)	**50.8 (8.5)**
Duration (years)	**42.1 (7.7)**
Sex (male, %)	**44.7%**
Updated (18-year) mean A1C (%)	**8.6 (0.96)**
A1 months	**1008.6 (495.5)**
Most recent A1C (%)	**7.4 (1.2)**
Serum creatinine (mg/dl)	**1.1 (0.83)**
eGFR (MDRD formula, mg/min)	**78.5 (23.7)**
Coronary Artery Calcification (CAC) score	**204 (377.6)**
Proliferative Retinopathy (PR) *	**54.4%**
Microalbuminuria **	**54.4%**
Overt Nephropathy***	**34.2%**
Coronary Artery Disease	**40.4%**
CAC Score ≥ 10 units	**47.6%**
Confirmed Distal Symmetrical Polyneuropathy (DSP) ****	**65.2%**
Lower Extremity Arterial Disease	**29.8%**

*Proliferative Retinopathy (PR) - Fundus photography 60+
** Microalbuminuria - albumin excretion rate >20 mg/min
***Overt Nephropathy - albumin excretion rate >200 mg/min
****Confirmed Distal Symmetrical Polyneuropathy (DSP) - DCCT clinical protocol

Results

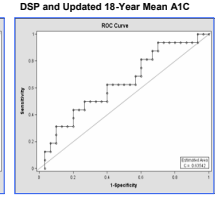
Prediction of complications:

DSP and Skin Intrinsic Fluorescence



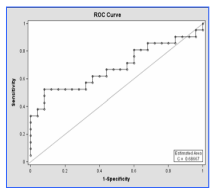
AIC = 47.7

DSP and Updated 18-Year Mean A1C



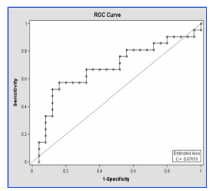
AIC = 60.7

PR and Skin Intrinsic Fluorescence



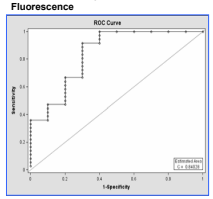
AIC = 67.0

PR and Updated Mean A1C



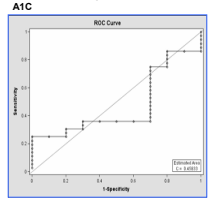
AIC = 64.4

Overt Nephropathy and Skin Intrinsic Fluorescence



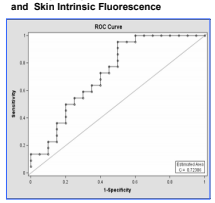
AIC = 34.1

Overt Nephropathy and Updated Mean A1C



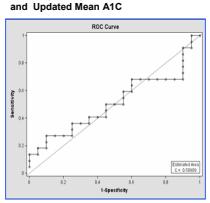
AIC = 52.2

Coronary Artery Calcification Score >10 and Skin Intrinsic Fluorescence



AIC = 51.0

Coronary Artery Calcification Score >10 and Updated Mean A1C



AIC = 62.1

Results

Table 2. Pearson correlation between skin intrinsic fluorescence and glycemic control/renal function in type 1 diabetes

Correlate	r	P-value
Current A1C	0.07	0.79
Update (18-Year) Mean A1C	0.03	0.83
A1 Months	0.06	0.70
eGFR (MDRD)	-0.40	0.006
Serum creatinine*	0.41	0.004

*Natural logarithmically transformed before analyses

Table 3. Association of skin intrinsic fluorescence with complications of type 1 diabetes

Complication	Intrinsic Fluorescence			18-year Mean HbA1c			A1 Months		
	OR*	p-value	MDRD adjusted p-value	OR*	p-value	MDRD adjusted p-value	OR*	p-value	MDRD adjusted p-value
Proliferative Retinopathy	1.22	0.53	0.94	1.73	0.10	0.14	2.69	0.02	0.03
Microalbuminuria	4.10	0.03	0.07	1.68	0.11	0.22	1.92	0.07	0.19
Overt Nephropathy	10.45	0.005	0.02	1.00	1.00	0.69	0.87	0.7	0.13
Coronary Artery Calcification Score>10	7.12	0.01	0.02	1.04	0.91	0.80	1.34	0.35	0.81
Coronary Artery Disease	1.33	0.36	0.74	1.18	0.58	0.66	1.48	0.21	0.37
Lower Extremity Arterial Disease	0.99	0.98	0.95	0.86	0.63	0.71	1.11	0.75	0.71
Confirmed Distal Symmetrical Polyneuropathy	18.12	0.007	0.009	1.73	0.12	0.22	3.51	0.01	0.02

*Data are presented as per standard deviation change in the predictor variable

Conclusion

Skin intrinsic fluorescence is associated with renal function, distal symmetrical polyneuropathy, and coronary artery calcification. Non-invasive skin fluorescence shows promise as an effective means to instantaneously assess the risk of diabetes related complications.