

Hemoglobin Glycation Index is Positively Associated with Skin Intrinsic Fluorescence

Dania L. Felipe MD¹, Shuqian Liu MD¹, James M. Hempe PhD¹, Nathaniel I. Matter PhD², John D. Maynard², Stuart Chalew MD¹

¹ LSU Health Sciences Center, Children's Hospital, New Orleans, LA. ² VeraLight, Inc., Albuquerque, NM.

Abstract

Our group previously reported that A1c levels are a function of mean blood glucose (MBG) and MBG-independent factors. The effect of MBG-independent factors on A1c can be quantified by the Hemoglobin Glycation Index (HGI) which is positively associated with risk for diabetes complications. As skin advanced glycation end products (AGEs) are positively associated with A1c, we hypothesized that skin AGE levels might also be influenced by MBG-independent factors measured by HGI. Skin intrinsic fluorescence (SIF) is a known surrogate of skin AGE levels. In this experiment, we examined relationships between skin fluorescence, A1c, HGI and MBG. We recruited 54 children (27 males) with type 1 diabetes, age 14±4 years, duration of diabetes 7±4 years, race (35 Caucasian, 19 African American) from the diabetes clinic at Children's Hospital of New Orleans. Skin AGEs were non-invasively assessed on the volar surface of the left forearm using a SCOUT DS system (Veralight, Albuquerque, NM) that measures SIF corrected for skin optical properties. MBG was derived from patient self monitored blood glucose meter data. A1c was measured at the same clinic visit by a National Glycohemoglobin Standardization Program (NGSP) certified immunoassay. HGI was calculated from A1c and MBG for each patient as previously described. The associations of HGI, A1c and MBG adjusted for patient age, gender, race, and duration of diabetes were analyzed in various linear regression models with SIF as the dependent variable. Multivariate analyses showed that A1c, HGI, gender and age were significantly (p<0.01) associated with SIF. Although MBG had a significant positive correlation with A1c (r=0.44, p<0.001), it was not a statistically important independent variable associated with SIF. These results suggest that MBG-independent factors measured by HGI have an important influence on glycation of both hemoglobin and skin proteins associated with risk for diabetes complications.

Introduction

Nonenzymatic-glycation of hemoglobin via the Maillard reaction forms A1c. The Maillard reaction leads to precursor substances which eventually become advanced glycation endproducts (AGEs). AGEs can deposit in multiple organs and may be associated with the development of microvascular complications¹. Measurement of skin intrinsic fluorescence (SIF) is a noninvasive method that estimates skin AGEs in vivo. Dermal fluorescence is correlated with AGEs measured directly from skin biopsies².

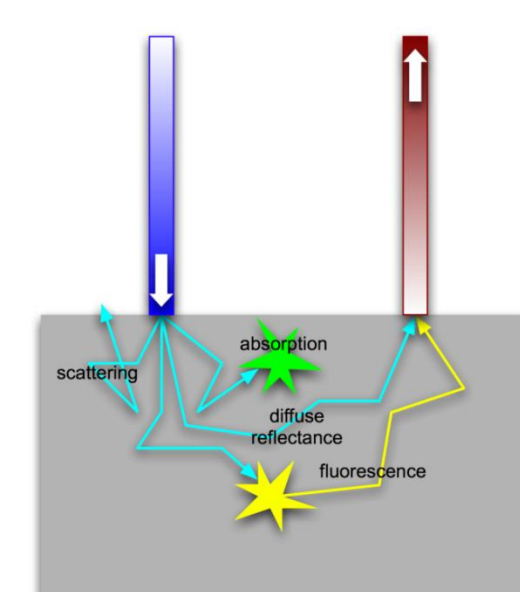
We have used a previously described novel Hemoglobin Glycation Index (HGI) to quantify biological variation in A1c that is not attributable to MBG levels³. Using the DCCT data, we have found that biological variation in hemoglobin A1c can predict the risk of developing nephropathy and retinopathy⁴.

We hypothesized that HGI, or A1c independent of MBG, would be associated with skin AGEs as measured by SIF in pediatric subjects with type 1 diabetes.

Figure 1 Veralight SCOUT DS



Figure 2. Fiber optic probe on SCOUT DS designed to collect fluorescence of dermal AGEs and cross-links



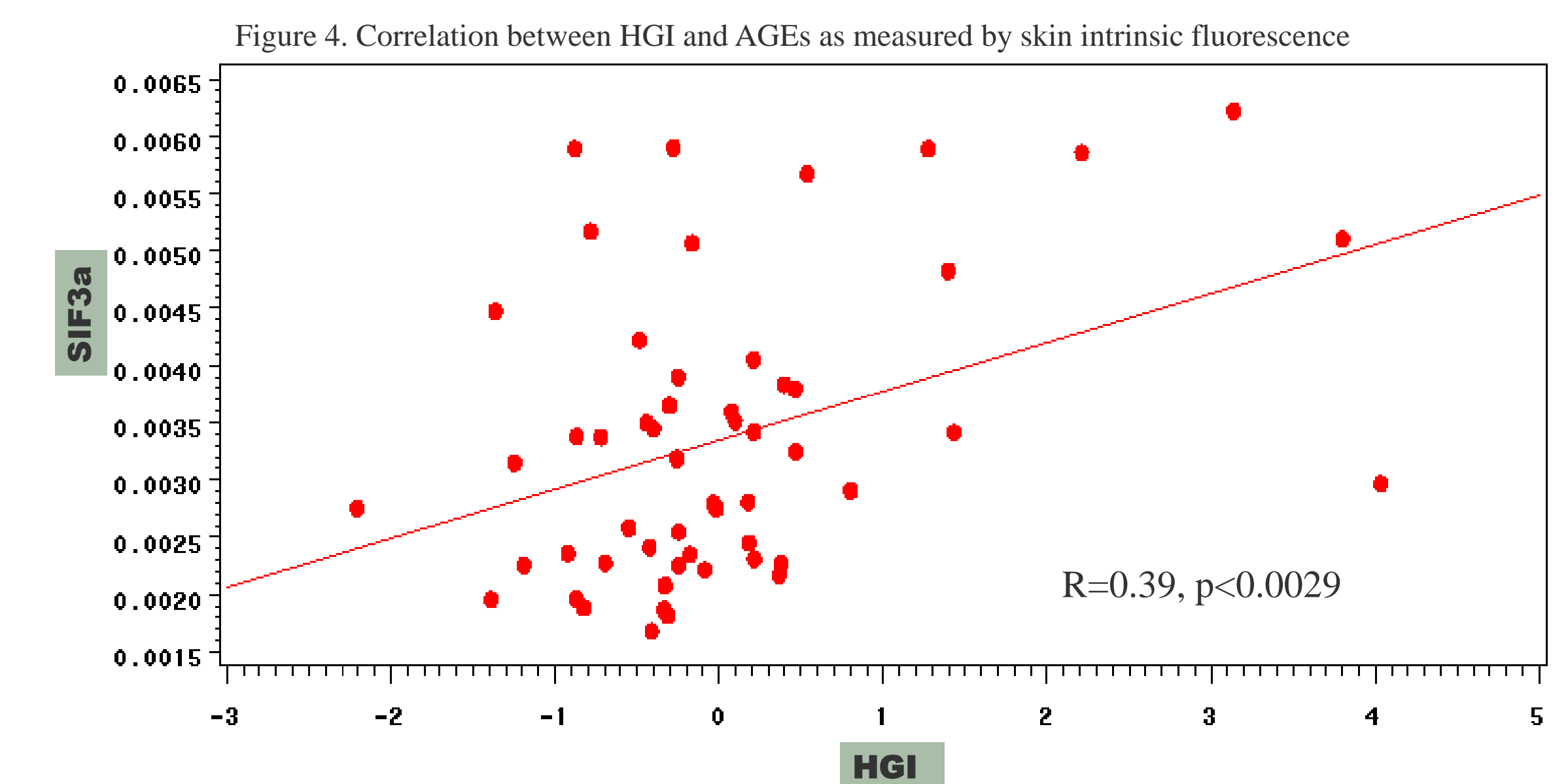
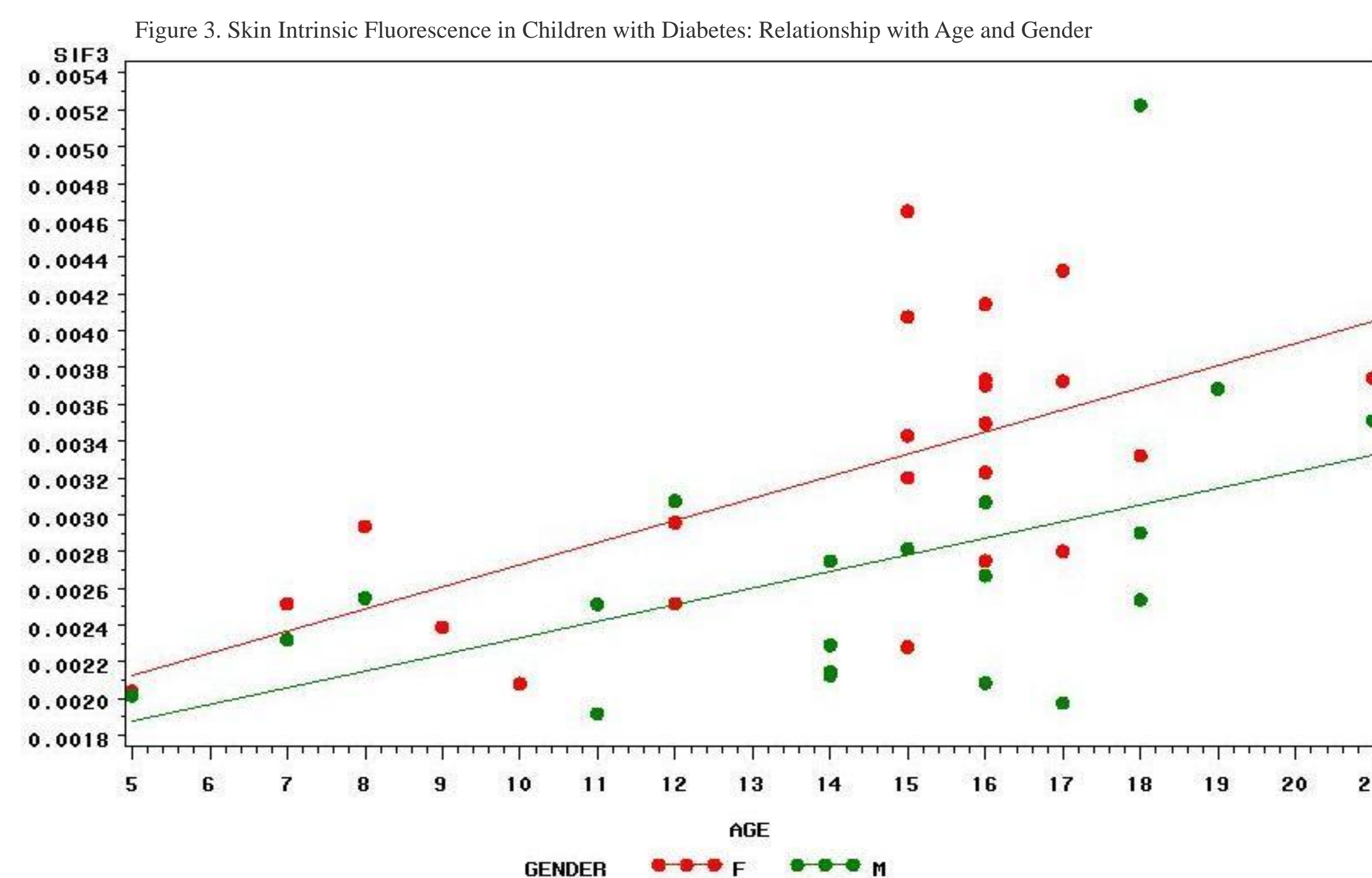
Methods

To test this hypothesis, we recruited 54 subjects (27 males) with type 1 diabetes from our Diabetes Clinic at Children's Hospital, New Orleans. Thirty-five of these subjects were Caucasian and 19 were African American. Mean age was 14.4±3.7 years and duration of diabetes (DOD) was 7.1±4 years. All the subjects recruited had been diagnosed for at least one year before participation. Using the SCOUT DS machine (Veralight, Inc. Albuquerque, NM, Fig. 1), SIF levels were measured on the volar surface of the left forearm. SCOUT DS excites AGE-related skin fluorescence with low-intensity ultraviolet and blue light. In addition, the instrument utilizes the measured diffuse reflectance to correct the emitted fluorescence for optical distortion of the skin. This intrinsic correction technique enables noninvasive fluorescence measurements in subjects with a wide range of factors such as melanin and hemoglobin content, skin thickness, and skin surface condition (Fig. 2).

MBG was calculated for each patient from glucose meter data at time of clinic visit from the previous 30 days. A1c was measured by a NGSP certified immunoassay. HGI was calculated at each visit from each patient's MBG and A1c. The influence of biological variation in A1c on skin SIF was evaluated in multivariate regression models using either HGI or A1c adjusted for MBG, age, gender, race, BMI, and DOD.

Results

We found that estimated AGE levels significantly increase with age (Fig.3). Female subjects with type 1 diabetes were found to have higher SIF levels than males (P<0.01) (Fig 3). MBG had a significant positive correlation with A1c (r=0.44, p<0.001), however, it was not a statistically important variable associated with SIF. Increases in HGI or A1c were statistically associated with increases in SIF (r=0.39, P<0.0029, Fig 4), even after adjustment for age, gender, race, and DOD.



Discussion

HGI, as a quantification of A1c, is an indicator of hemoglobin glycation differences between individuals not due to MBG. Our study shows that there is a significant association of HGI, or A1c controlled for MBG, with SIF. However, SIF was not associated with MBG levels.

SIF is a marker of dermal AGEs. AGEs have been associated with the development of diabetes microvascular complications. Our findings suggest that individual differences in glycation not due to MBG may influence AGE burden in the skin and perhaps other tissues. Differential formation of AGEs may be a mechanism for differences in risk for microvascular complications in type 1 diabetes subjects.

References

- 1) Genuth et al. Glycation and Carboxymethyllysine Levels in Skin Collagen Predict the Risk of Future 10-Year Progression of Diabetic Retinopathy and Nephropathy in the DCCT and EDIC Participants with Type 1 Diabetes. *Diabetes*, 54:3103-3111 (2005).
- 2) Meerwaldt et al. Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia*, 47:1324-1330 (2004).
- 2) Hempe et al. High and low hemoglobin glycation phenotypes in type 1 diabetes: A challenge for interpretation of glycemic control. *J Diabetes Complications*, 16:313-320, (2002).
- 3) McCarter et al. Biological Variation in A1c Predicts Risk of Retinopathy and Nephropathy in Type 1 Diabetes. *Diabetes Care*, 27:1259 (2004).