

# Noninvasive Measurement of Advanced Glycation End Products Correlates with Macrovascular Complications in Patients with Type 1 and Type 2 Diabetes

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## ABSTRACT

Advanced glycation end products (AGEs) are implicated in the development of cardiovascular disease and are thought to induce vascular stiffness, endothelial dysfunction and inflammation. Skin AGEs can be assessed noninvasively via skin intrinsic fluorescence (SIF). We hypothesized that SIF could detect the presence or absence of macrovascular complications in a cross-sectional analysis of patients with type 1 or type 2 diabetes.

SIF was obtained in 202 subjects with type 1 (n=58) or type 2 (n=32) diabetes followed at the MedStar Research Institute for an average of 9.0 years or Pittsburgh Epidemiology of Diabetes Complications Study in type 1 diabetes (n=112) for an average of 21 years. Detailed history was obtained from the subjects and medical record review. SIF was determined on the volar forearm and internally adjusted for subject age, light scattering, melanin and hemoglobin content. Analysis of variance was performed to compare SIF, mean A1c, and last A1c with the presence or absence of specific macrovascular complications. ROC curves were used to compare the ability to detect macrovascular complications. Coronary artery disease (CAD) included proven MI, revascularization, and clinic physician diagnosed angina.

SIF was significantly higher in individuals with CAD than without ( $0.55 \pm 0.25$  vs  $0.42 \pm 0.18$ ,  $p=0.0001$ ) with an area under the ROC curve (AUC) of 0.67. SIF was also higher in individuals with peripheral vascular disease (PVD) than without ( $0.57 \pm 0.2$  vs  $0.43 \pm 0.2$ ,  $p=0.0002$ ,  $AUC=0.70$ ). Mean A1c over time correlated with CAD ( $p=0.002$ ,  $AUC=0.66$ ) and PVD ( $p \leq 0.009$ ,  $AUC=0.65$ ), as predicted by long-term studies such as DCCT and UKPDS. SIF correlated with mean A1c ( $p=5.0e-10$ ,  $R=0.42$ ). Last A1c did not correlate with CAD or PVD.

SIF was able to distinguish the presence or absence of macrovascular complications, providing a spot measurement reflecting years of longitudinal A1c measurements. Last A1c did not provide any information on macrovascular complications. Additional prospective studies are warranted to evaluate the potential of SIF to provide prognostic cardiovascular information to guide therapy.

## BACKGROUND

- Chronic hyperglycemia leads to increased risk of macrovascular and microvascular complications [1]
- Advanced glycation end products (AGEs) accumulate in tissues affected by diabetes and predict progression of diabetes-related complications [2, 3]
- AGEs may promote cardiovascular disease by inducing vascular stiffness, endothelial dysfunction, inflammation, or lipid abnormalities [4]
- AGE levels are increased in patients with diabetes with coronary heart disease, peripheral arterial occlusive disease, and heart failure, and may be predictive of mortality [4, 5]
- Skin AGEs can be detected noninvasively by spectroscopic assessment of skin intrinsic fluorescence [6, 7]

## STUDY AIM

To evaluate the relationship between AGE-derived skin intrinsic fluorescence (SIF) and macrovascular complications in a cross-sectional analysis of two well-characterized populations with type 1 and type 2 diabetes.

## METHODS

Noninvasive assessment of skin intrinsic fluorescence was performed using an investigational skin fluorescence spectrometer device (VeraLight, Inc.):

- Volar forearm illuminated with blue and white light
- Skin intrinsic fluorescence internally adjusted for participant age, light scattering, melanin, and hemoglobin content
- Macrovascular complications obtained from interviews and medical history reviews:
  - Coronary artery disease (CAD) defined as:
    - Angina, or
    - Myocardial infarction, or
    - Revascularization
  - Peripheral vascular disease (PVD)



Figure 1: Noninvasive assessment of skin AGEs using a skin fluorescence spectrometer

Table 1: Characteristics of the Study Cohorts

	MedStar Research Institute Clinical Practice	Univ. of Pittsburgh Epidemiology of Diabetes Complications (EDC) Study
Background	Patients with type 1 or type 2 diabetes followed for a mean duration of 10 years (range: 4 to 25 years).	A 20-year prospective study of a well-defined cohort with childhood-onset type 1 diabetes.
# of Participants	94	102
Mean Age	55	48
Male/Female	47/47	46/56
Diabetes Type	58 Type 1 33 Type 2 3 Other	102 Type 1
Median Duration	23 years	39 years

## RESULTS

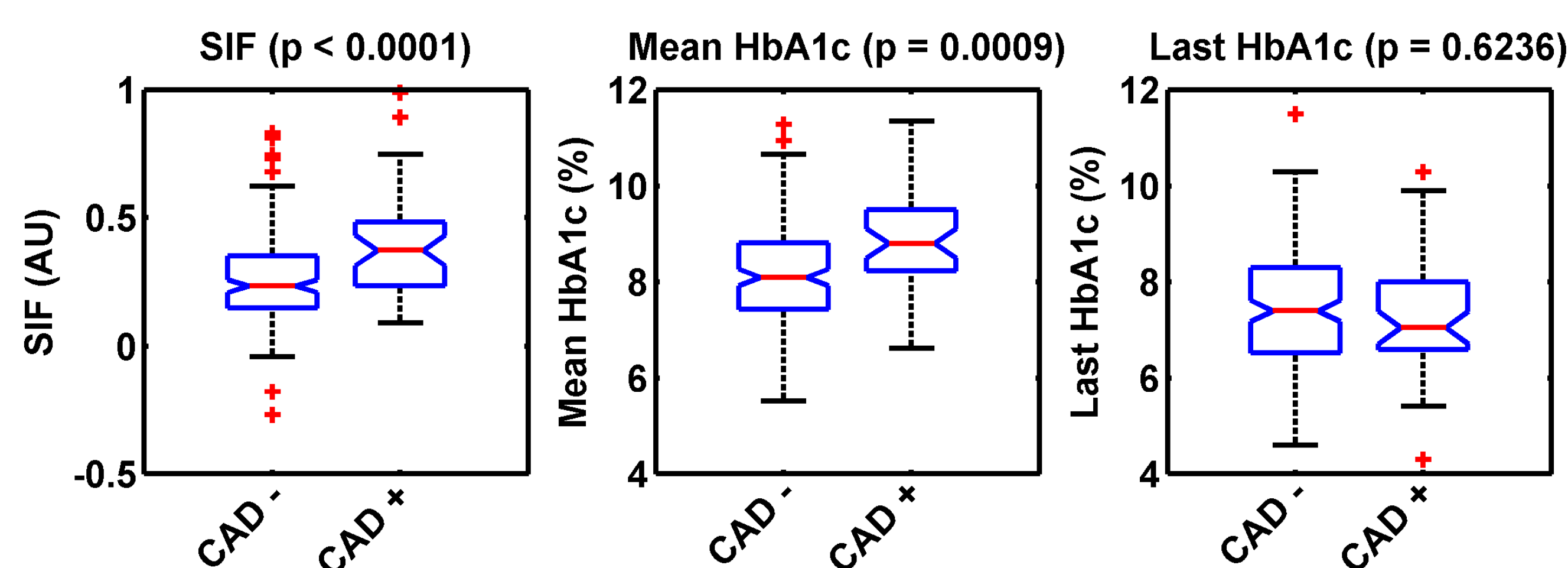


Figure 2: SIF and historical mean HbA1c were significantly higher in individuals with CAD compared to those without CAD. In contrast, the last HbA1c did not differentiate the groups.

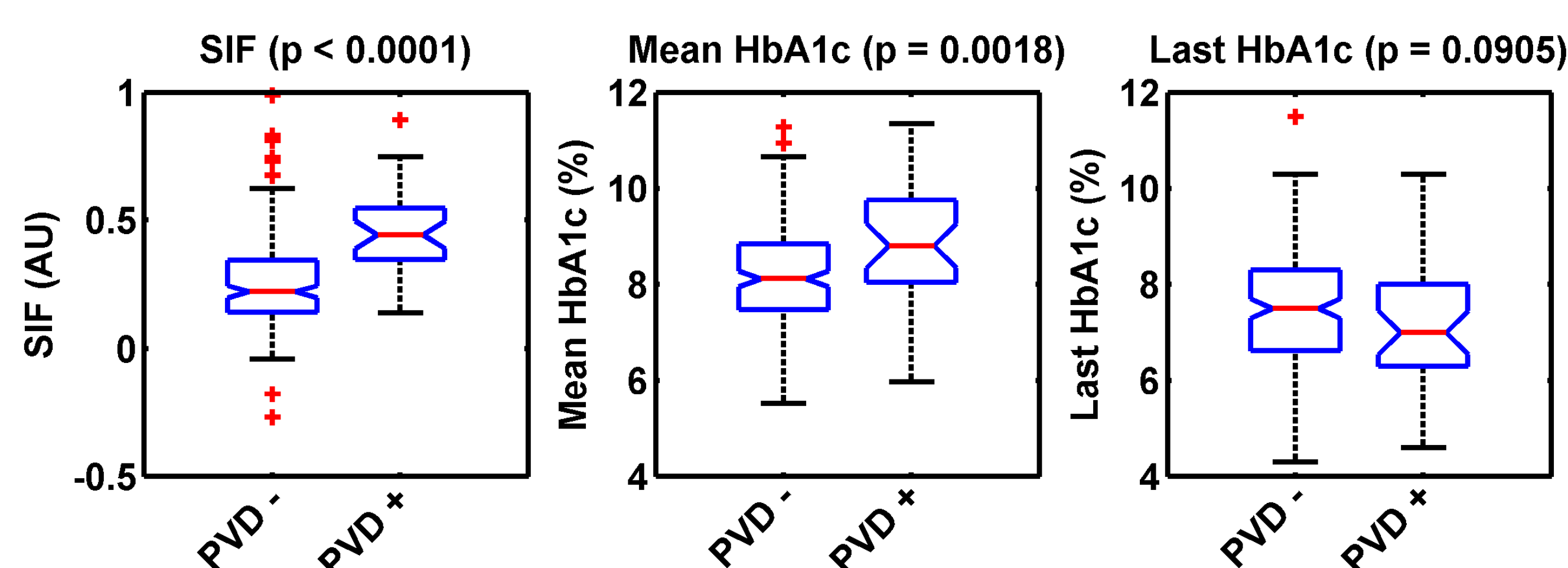


Figure 3: SIF and historical mean HbA1c were significantly higher in individuals with PVD compared to those without PVD. In contrast, the last HbA1c did not differentiate the groups.

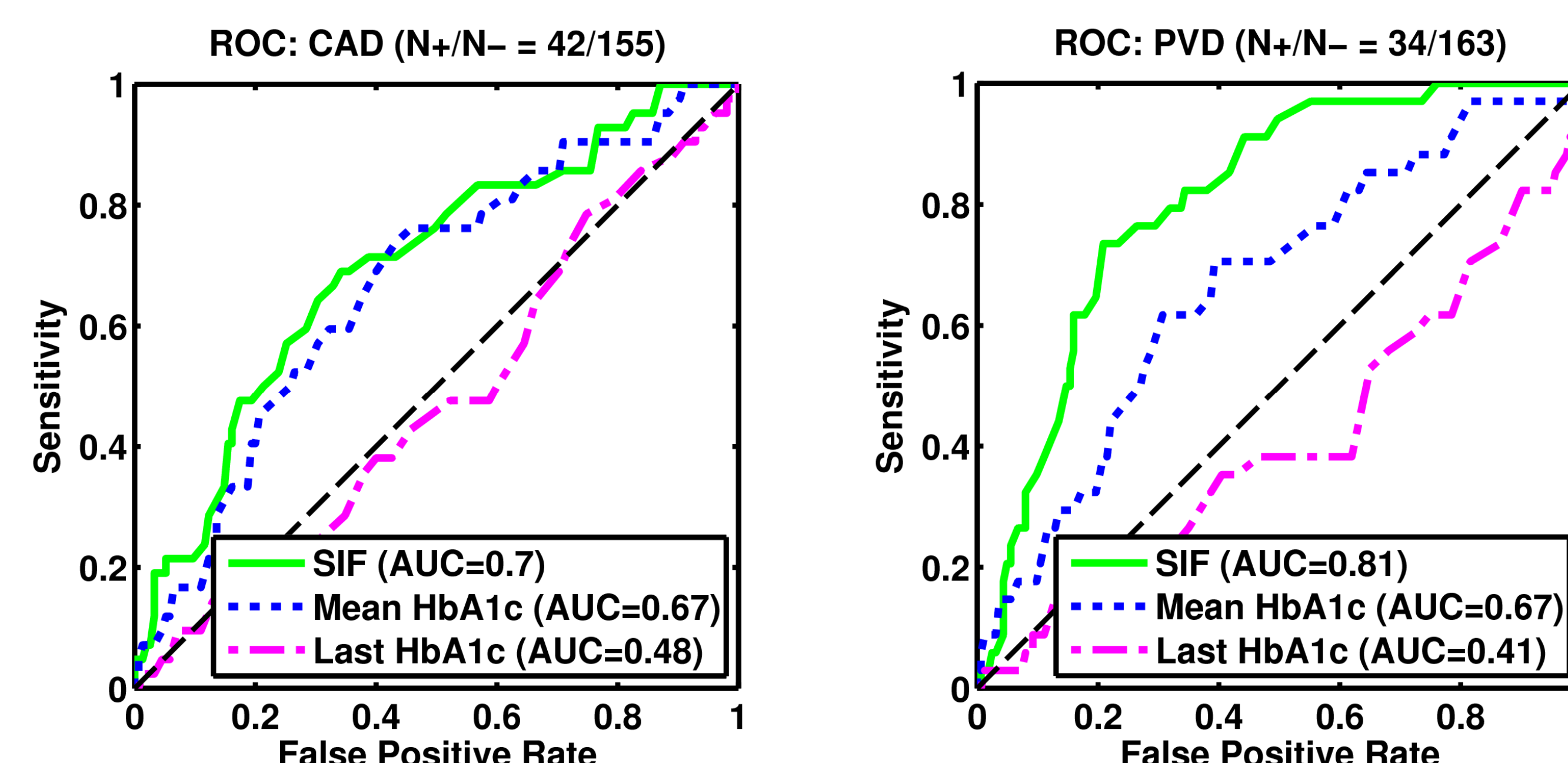


Figure 4: The ability of skin intrinsic fluorescence, historical mean HbA1c, and last HbA1c to distinguish disease state. SIF was able to distinguish CAD or PVD disease state with high sensitivity. The last HbA1c did not differentiate the presence or absence of CAD or PVD.

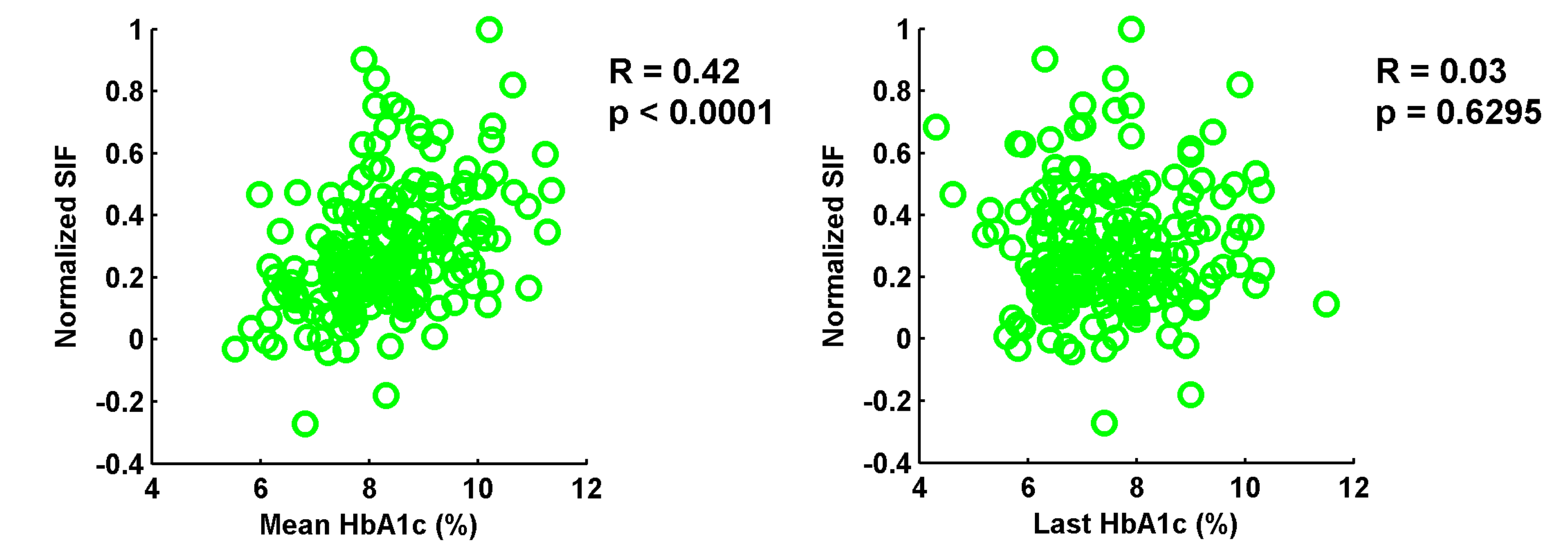


Figure 5: SIF and historical mean HbA1c were significantly correlated while SIF and last HbA1c were not.

## SUMMARY

- A single measure of HbA1c does not indicate the presence or history of macrovascular complications (CAD, PVD) in patients with diabetes
- Historical mean HbA1c, which requires knowledge of long-term HbA1c measurements, provides an overall picture of hyperglycemia and indicates the presence or history of macrovascular complications (CAD, PVD) in patients with diabetes
- Noninvasive assessment of AGE-influenced skin intrinsic fluorescence indicates the presence or history of macrovascular complications (CAD, PVD) in patients with diabetes, and is significantly better correlated with PVD than historical mean HbA1c.

## CONCLUSIONS

- Skin fluorescence provides a noninvasive assessment of the level of tissue accumulation of advanced glycation end products, representing cumulative glycemic and oxidative stress.
- A single measure of HbA1c provides little information in ascertaining the risk of diabetes-related macrovascular complications.
- Noninvasive assessment of AGE-influenced skin intrinsic fluorescence indicates the presence or history of macrovascular complications (CAD, PVD) in patients with diabetes, and is significantly better correlated with PVD than either historical mean HbA1c or last HbA1c.

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