Journal of Diabetes Science and Technology
Volume 7, Issue 4, July 2013

ORIGINAL ARTICLE

Noninvasive Skin Fluorescence Spectroscopy Is Comparable to Hemoglobin A1c and Fasting Plasma Glucose for Detection of Abnormal Glucose Tolerance

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Abstract

Aim:

We compare performance of noninvasive skin fluorescence spectroscopy (SFS), fasting plasma glucose (FPG), and hemoglobin A1c (A1C) for detection of abnormal glucose tolerance (AGT).

Methods:

The NSEEDS trial evaluated SFS, FPG, and A1C in an at-risk population of 479 previously undiagnosed subjects from nine US centers, each of whom received a 75 g, 2 h oral glucose tolerance test (OGTT). Skin fluorescence spectra were collected and analyzed with SCOUT DS® devices. Disease truth was AGT, defined as OGTT ≥140 mg/dl. Abnormal glucose tolerance sensitivity, false positive rate (FPR), and receiver operating characteristic (ROC) curves were computed for each measurement technique. Skin fluorescence spectroscopy reproducibility was also assessed.

Results:

The AGT sensitivity of SFS was 68.2%, higher than that of FPG (thresholds of 100 and 110 mg/dl) and A1C (thresholds of 5.7% and 6.0%). The FPR of SFS was 37.7%, comparable to A1C at the 5.7% threshold (30.7%). Partial ROC areas of SFS, FPG, and A1C were similar for FPRs of 20–50% (average sensitivities of 64.0%, 59.0%, and 68.6%, respectively). The interday coefficient of variation for SFS was 7.6%.

Conclusions:

Skin fluorescence spectroscopy has similar screening performance to FPG and A1C and is a viable approach for detection of AGT.

J Diabetes Sci Technol 2013;7(4):990–1000

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Abbreviations: (A1C) hemoglobin A1c, (ADA) American Diabetes Association, (AGT) abnormal glucose tolerance, (AUC) area under the curve, (BMI) body mass index, (CV) coefficient of variation, (FPG) fasting plasma glucose, (FPR) false positive rate, (IGT) impaired glucose tolerance, (NGT) normal glucose tolerance, (OGTT) oral glucose tolerance test, (pAUC) partial area under the curve, (ROC) receiver operating characteristic, (SDS) SCOUT diabetes score, (SFS) skin fluorescence spectroscopy

Keywords: abnormal glucose tolerance, diabetes screening, fluorescence, noninvasive, SCOUT DS

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Introduction

Effective diabetes screening programs are an essential component of primary disease prevention. While blood-based indicators of glycemia are commonly used to screen for type 2 diabetes, these methods presents challenges that limit the fraction of the at-risk population that is tested.[1] For example, the need for overnight fasting and the turnaround times associated with laboratory processing of blood samples represent barriers to implementing effective diabetes screening programs.[2] While laboratory-based hemoglobin A1c (A1C), which requires no fasting, is increasingly used as a screening tool,[3] the test still requires drawing venous blood and waiting for results to be reported to the physician. Research has found that risk stratification using a noninvasive screening measure increases participation in confirmatory blood-based testing[4,5] and that such screening approaches are most cost-effective with respect to the cost per identified case of disease.[6]

Diabetes screening based on noninvasive skin fluorescence spectroscopy (SFS) has been proposed.[7–9] The SCOUT DS device (VeraLight, Albuquerque, NM) uses SFS to noninvasively measure biomarkers of diabetes in the skin, including fluorescent advanced glycation end products such as pentosidine and cross-lines as well as indicators for cell metabolism and oxidative stress such as reduced nicotinamide adenine dinucleotide and flavin adenine dinucleotide.[10,11] The device illuminates the skin of the volar forearm (**Figure 1**) with low-intensity light at a variety of near-ultraviolet and visible wavelengths. As skin tone varies across subjects because of melanin and hemoglobin concentrations plus light scattering, the intensity and duration of the excitation light is automatically adjusted by the SCOUT device for each subject to compensate for the attenuation of the excitation light and emitted fluorescence. The measured optical signals are then analyzed for fluorescence related to the development of prediabetes and diabetes and a SCOUT diabetes score (SDS) is produced.

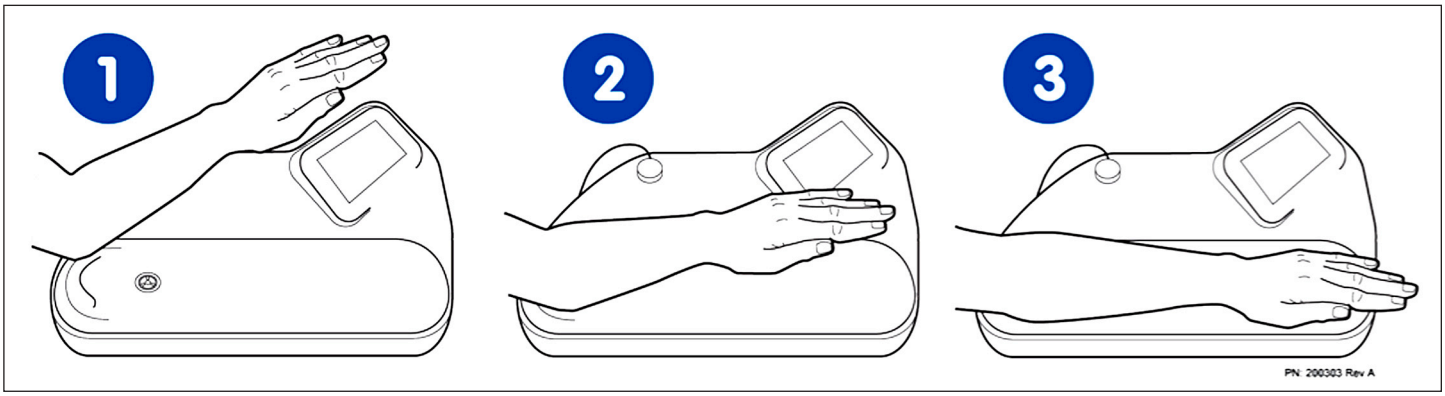

Figure 1. Forearm insertion sequence on SCOUT DS.

Skin fluorescence spectroscopy measurements do not require fasting or blood handling and generate results immediately at the point of service. The score output by the SCOUT DS device is reported on a scale of 0 to 100, with higher SDS values indicating higher disease probability. Subjects with SDS ≥ 50 are typically considered to have screened positively and are referred for a follow-up blood test to make a diagnosis of prediabetes or type 2 diabetes. In previous studies of the SCOUT DS device, SFS has been found to have superior sensitivity to fasting plasma glucose (FPG) and A1C for detection of abnormal glucose tolerance (AGT).[12,13] The work presented here is a further investigation and prospective multicenter validation of the AGT screening performance of SFS.

Methods

Objectives

The NSEEDS trial was a prospective multicenter validation of SFS screening performance in an at-risk population using the SCOUT DS platform (*clinialtrials.gov*, NCT01375686). Fasting plasma glucose and A1C were used as comparative

screening methods. Disease truth was AGT, defined as a postchallenge plasma glucose of at least 140 mg/dl after a 75 g, 2 h oral glucose tolerance test (OGTT). An additional objective of the trial was to assess the interday/intraday and interdevice/intradevice reproducibility of SDS values.

Subjects

Subjects at risk for prediabetes and/or type 2 diabetes were recruited using clinical databases and advertising from nine research centers distributed across the United States. The study protocol was approved by the Schulman Associates institutional review board and encompassed all centers. Informed consent was obtained from all study participants.

Inclusion criteria were (*i*) age greater than or equal to 45 years or (*ii*) age 18 to 44 years with a body mass index (BMI) > 25 kg/m^2 and one or more additional American Diabetes Association (ADA) defined risk factors for type 2 diabetes.[14] Subjects with a prior diagnosis of any type of diabetes, previous participation in trials of the SFS device, known skin photosensitivity, pregnancy, prior bariatric surgery, dialysis or known renal compromise, or participation in any investigational treatments were excluded.

Study Design and Data Collection

Each center was supplied with two SFS instruments (SFS A and SFS B). Using the operator's manual, center staff were trained to explain to study participants how to seat themselves at the device and to place their arms on the optical sensor. The SFS devices performed automated quality control and self-calibration checks as needed when subject measurements were not being performed.

Each subject made two visits to the center with at least one day separating each visit (**Figure 2**). The mean intervisit separation was 4.5 days, with a standard deviation of 4.1 days.

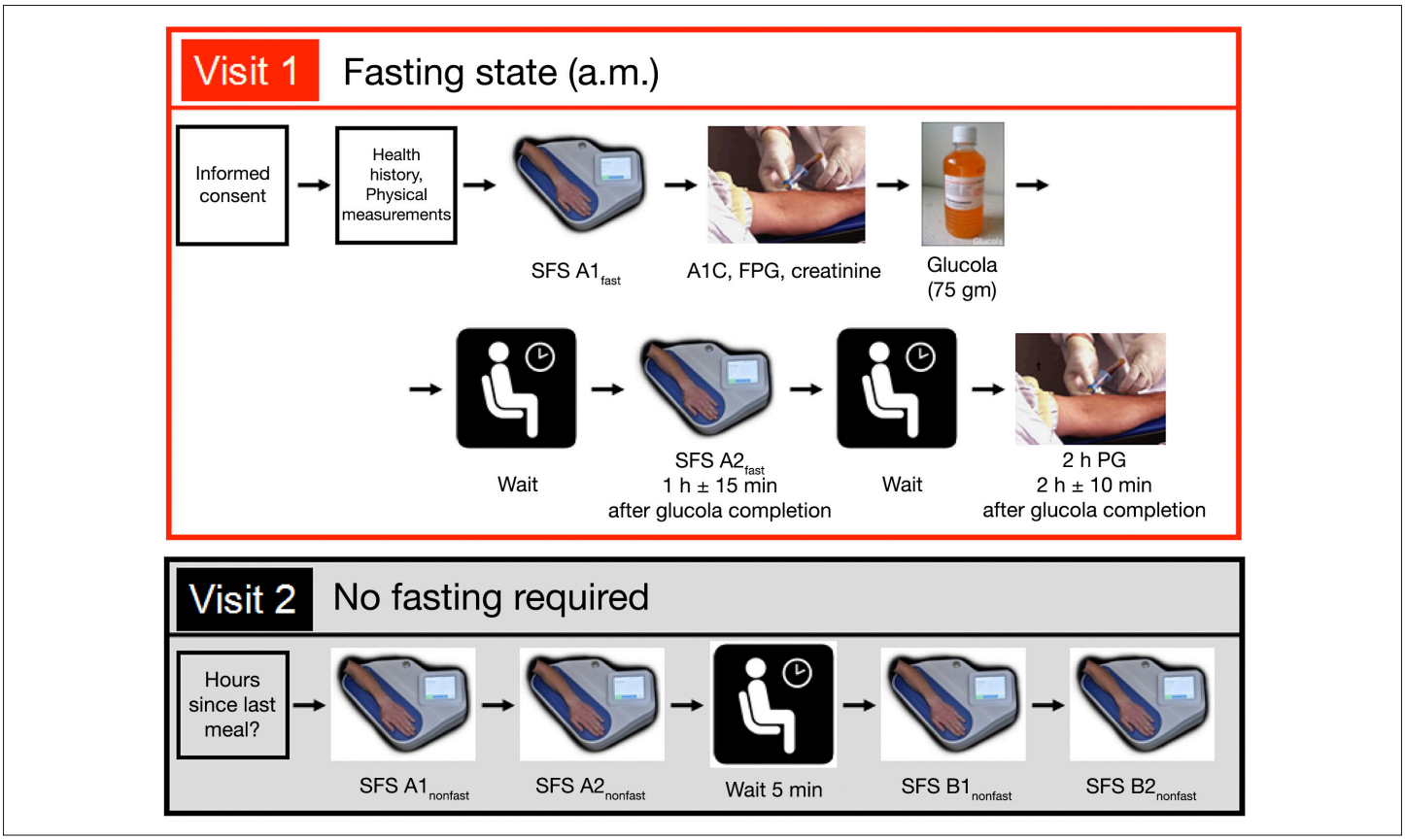

Figure 2. Visit flow diagram for the NSEEDS study. PG, plasma glucose.

On visit 1, subjects reported to the study center in the morning after an overnight fast of at least 8 h. Informed consent was obtained for all subjects. Each subject completed a short health history and had physical measurements of height, weight, waist circumference (at the midpoint between the top of the iliac crest and inferior margin of the last rib), and blood pressure. After completing an SFS measurement on device A (SFS $A1_{fast}$), venipuncture was performed to collect FPG and A1C specimens. The subject then consumed a 75 g oral glucose load (glucola, 10 fl oz) within 5 min. Two hours ±10 min after consumption, a venipuncture was performed to collect the 2 h postchallenge plasma glucose specimen.

On visit 2, subjects reported any time of day in a nonfasting state to test SFS in its intended-use environment. After recording the number of hours since the subject's last meal, two visit 2 SFS measurements were collected on device A (SFS $A1_{nonfast}$ and SFS $A2_{nonfast}$). Two additional visit 2 SFS measurements were collected on device B (SFS $B1_{nonfast}$ and SFS $B2_{nonfast}$).

Because it represents the intended use of SFS in clinical practice, the first nonfasting SFS measurement (SFS $A1_{nonfast}$) was used for primary analyses of SFS detection of AGT. Other SFS measurements described earlier were used to assess the between- and within-device variation of SFS scores and to examine any effects of fasting on SFS performance.

Analytical Methods

The Scout DS device measures light in the range of 360 to 660 nm from the skin of left volar forearm approximately 3 in. below the elbow (**Figure 1**) and excites fluorescence with light emitting diodes centered at 375, 405, 417, 435, and 456 nm. The device also measures reflectance with a white light emitting diode to account for subject-specific melanin and hemoglobin content plus light scattering. Taking into account subject age, gender, and skin reflectance, the resulting optical signals were then analyzed by multivariate fluorescence spectroscopy to produce the SDS (0 to 100 scale).

All blood assays were acquired by venipuncture. Hemoglobin A1c was collected in ethylenediaminetetraacetic acid vacutainer tubes, mixed immediately by repeated gentle inversion, and then refrigerated. The A1C assays were traceable to the National Glycohemoglobin Standardization Program.

Plasma glucose blood samples were collected in lithium heparin plasma-separator vacutainer tubes, mixed by gentle inversion, and immediately centrifuged at 2000 g for 15 to 20 min. Aliquots of plasma specimens were placed in transfer tubes and refrigerated. Glucose assays utilized either the glucose oxidase or hexokinase method.

Fasting plasma glucose and A1C specimens were analyzed by a local reference laboratory selected by the clinical center. Local reference laboratories were accredited by the College of American Pathology and certified in compliance with the Clinical Laboratory Improvements Amendments. Each laboratory participated in College of American Pathology proficiency testing and provided the results of the proficiency testing for the laboratory tests being performed for the study. All assays had to be judged as acceptable by the College of American Pathology.

To ensure consistent determination of disease status for all study participants, 2 h plasma glucose specimens were sent to a central reference laboratory (Advance Research and Diagnostic Laboratory, University of Minnesota Medical Center).

Performance Assessment

The device's algorithm for computing SDS values and routines for assuring the quality of acquired spectra and ongoing system calibration were developed with independent algorithm training data. All algorithms and associated parameters were fixed prior to data acquisition. Results reported in this work are fully prospective.

Point estimates and 95% confidence intervals on the sensitivity and false positive rate (FPR) for the detection of AGT were calculated for FPG, A1C, and SFS. Receiver operating characteristic (ROC) curves were generated for each test. The area under the ROC curve [area under the curve (AUC)] and partial area under the curve (pAUC) for FPRs in the range of 0.2–0.5 were also computed for each test. The range for the pAUC computation was determined from a

literature review of the FPR of the FPG test for detection of AGT in large cohorts of at-risk, previously undiagnosed subjects at the ADA-recommended cut point of 100 mg/dl.[15–18] Partial ROC areas were computed per Dodd and Pepe.[19] Confidence intervals on the AUC and pAUC were determined as described by Qin and coauthors.[20]

Various aspects of SDS reproducibility were assessed. Reproducibility was expressed as the coefficient of variation (CV) from the Hoorn study.[21] Statistical analyses were performed with MATLAB 7.5 (R2007b).

Results

Data Description

Refer to **Figure 3** for a data accounting summary. A total of 510 subjects enrolled in the NSEEDS trial. Of the enrolled subjects, 22 subjects were screen failures due to inability to collect an OGTT blood specimen, inability to complete the 75 g glucose challenge, or other laboratory errors. An additional 3 subjects received 2 h OGTT blood draws that were outside the allowable 2 h ± 10 min window, leaving a total of 485 subjects with complete blood reference data. In addition, 6 subjects were lost to follow-up and did not complete the two-visit sequence of the NSEEDS trial, leaving a total of 479 subjects who completed the entire protocol.

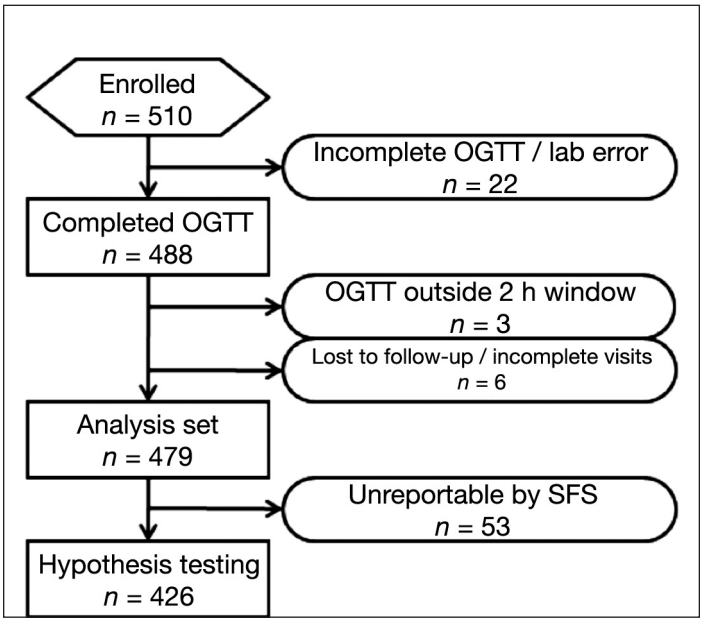

Figure 3. Data accounting summary for the NSEEDS study.

The SFS device was able to obtain a valid SFS $A1_{nonfast}$ measurement from 426 of the 479 subjects who completed the NSEEDS study. Failure to obtain a valid SFS measurement resulted from inconsistent spectra between the two arm insertions that comprised a complete SFS measurement (n = 47) or data that were inconsistent with the algorithm development data set (n = 6). All outlier metrics and thresholds were prespecified and developed exclusively with the independent, previously acquired algorithm training data. Thus, 426 subjects had complete sets of SFS data and blood test data available for analysis.

Cohort Description

The demographic characteristics of the 426 subjects in the analysis set are summarized in **Table 1**. The AGT prevalence was 25.8%. The AGT and normal glucose tolerance (NGT) groups had similar distributions of age, gender, and family histories of diabetes. Subject BMI, hypertension rate, and waist circumference (females only) were significantly higher in subjects with AGT versus NGT. The ethnicities of the AGT and NGT groups differed (p = .005). Relative to the NGT group, the AGT group had a larger fraction of Latinos (34% versus 24%) and a smaller fraction of African Americans (5% versus 15%).

Screening Performance Comparison

Because SFS is intended to allow testing at any time of day without regard to fasting status, the primary analysis compared SFS screening performance from the nonfasting visit (visit 2) to that of FPG. The AGT ROC curves for SFS (SFS $A1_{nonfast}$; blue/solid line), FPG (red/dashed line), and A1C (green/dash–dotted line) are shown in **Figure 4**. Points indicate performance of the tests at their respective screening thresholds of 50 (SFS; blue circle), 100 mg/dl (FPG; solid red square), 110 mg/dl (FPG; open red square), 5.7% (A1C; solid green triangle), and 6.0% (A1C; open green triangle). While the ROC curves for FPG and A1C indicate higher sensitivity than SFS at the lowest FPRs, the ROC curves for SFS and A1C are nearly overlapping for FPR > 0.3. Relative to FPG, both A1C and SFS exhibit higher AGT sensitivity in this region of the ROC curve.

Table 1.
Demographic Characteristics of All NSEEDS Subjects in the Analysis Set (i.e., Those Measureable by Skin Fluorescence Spectroscopy) with Normal Glucose Tolerance versus Abnormal Glucose Tolerance[a]

		NGT n = 316 (74%)		AGT n = 110 (26%)		p value
Gender	Male	142	(45%)	42	(38%)	0.218[b]
	Female	174	(55%)	68	(62%)	
Ethnicity	White	188	(59%)	64	(58%)	0.005[b]
	Latino	76	(24%)	37	(34%)	
	African American	48	(15%)	5	(5%)	
	Other	4	(1%)	4	(4%)	
Parent with diabetes		104	(33%)	45	(41%)	0.130[b]
Sibling with diabetes		44	(14%)	18	(16%)	0.532[b]
Hypertensive		63	(20%)	40	(36%)	0.001[b]
Age (years)		49.9 ± 13.9		52.6 ± 11.7		0.156[c]
BMI (kg/m^2)		30.0 ± 6.3		33.3 ± 7.5		< 0.001[c]
Waist, male (in.)		40.1 ± 5.7		40.9 ± 4.3		0.281[c]
Waist, female (in.)		37.5 ± 5.9		42.3 ± 6.8		< 0.001[c]
2 h glucose on OGTT (mg/dl)		102.2 ± 22.4		207.7 ± 98.0		N/A[d]
FPG (mg/dl)		93.5 ± 8.9		115.7 ± 50.6		< 0.001[c]
A1C (%)		5.5 ± 0.3		6.4 ± 1.8		< 0.001[c]
A1C (mmol/mol)		36.7 ± 3.3		46.3 ± 19.6		< 0.001[c]
SFS		48.0 ± 9.1		54.1 ± 9.5		< 0.001[c]

[a] Values are expressed as either number (%) or mean ± standard deviation.
[b] Pearson's χ^2 test.
[c] Wilcoxon rank sum test.
[d] AGT and NGT groups were stratified on the basis of an OGTT threshold of 140 mg/dl.

Table 2 is a summary of the AUC, pAUC, sensitivity, and FPR for SFS and the FPG and A1C tests using the screening thresholds depicted in **Figure 4**. The AGT sensitivity of SFS at its decision threshold of 50 arbitrary units was higher than FPG at the 100 and 110 mg/dl thresholds and A1C at the 5.7% and 6.0% thresholds. The AGT FPR of SFS was higher than FPG but comparable to A1C at a 5.7% threshold. The pAUCs for $0.2 \leq FPR \leq 0.5$ for A1C and SFS were 0.206 and 0.192, respectively (corresponding to average sensitivities of 68.7% and 64.0%). The corresponding pAUC for FPG was 0.177 (average sensitivity = 59.0%).

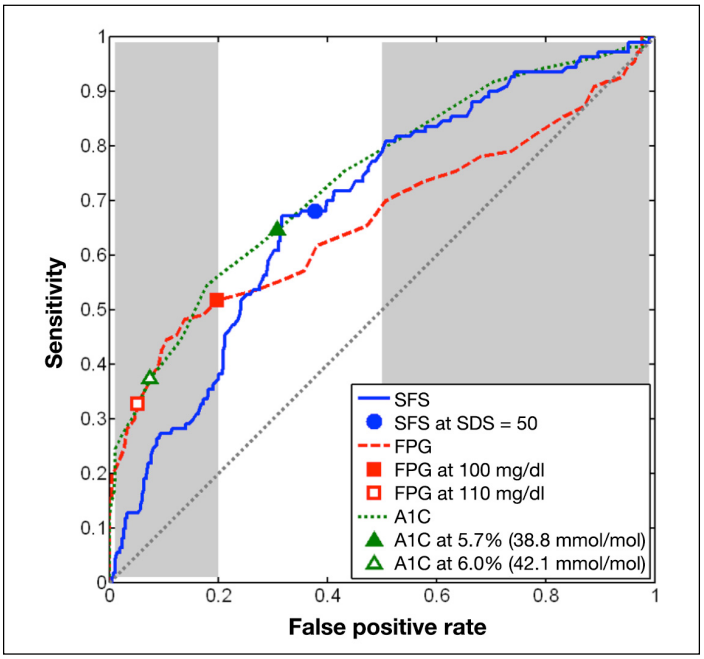

Figure 4. NSEEDS study ROC curves for detection of AGT for SFS (SFS A1nonfast), FPG, and A1C. Vertical lines denote FPR = 0.2 and FPR = 0.5, which are the limits used for partial ROC area computations in **Table 2**.

Figure 5 presents paired SDS values by subject under various test–retest conditions. Data pairs in panel A reflect SFS measurements collected on the same day (visit 2, nonfasting) on a common instrument (device A; measurement 2 versus measurement 1; Hoorn CV = 5.5%). The intraday CV shown in panel A did not vary significantly by ethnicity or skin tone (data not shown). Data pairs in panel B correspond to measurements collected on the same day (visit 2, nonfasting) but with different SFS instruments (device B versus device A; Hoorn CV = 6.9%).

Table 2.
Summary of Screening Test Performance Metrics

Test	AGT AUC (95% CI)	AGT pAUC 0.2 ≤ FPR ≤ 0.5 (95% CI)	Threshold	AGT FPR (%; 95% CI)	AGT Sensitivity (%; 95% CI)
SFS	0.692 (0.635–0.749)	0.192 (0.161–0.223)	50	37.7 (32.5–43.1)	68.2 (59.0–76.1)
FPG	0.668 (0.602–0.734)	0.177 (0.147–0.207)	100 mg/dl	19.3 (15.3–24.0)	51.8 (42.6–60.9)
			110 mg/dl	5.1 (3.1–8.1)	32.7 (24.7–41.9)
A1C	0.744 (0.692–0.795)	0.206 (0.170–0.242)	5.7% (38.8 mmol/mol)	30.7 (25.9–36.0)	64.5 (55.3–72.9)
			6.0% (42.1 mmol/mol)	7.3 (4.9–10.7)	37.3 (28.8–46.6)

CI, confidence interval.

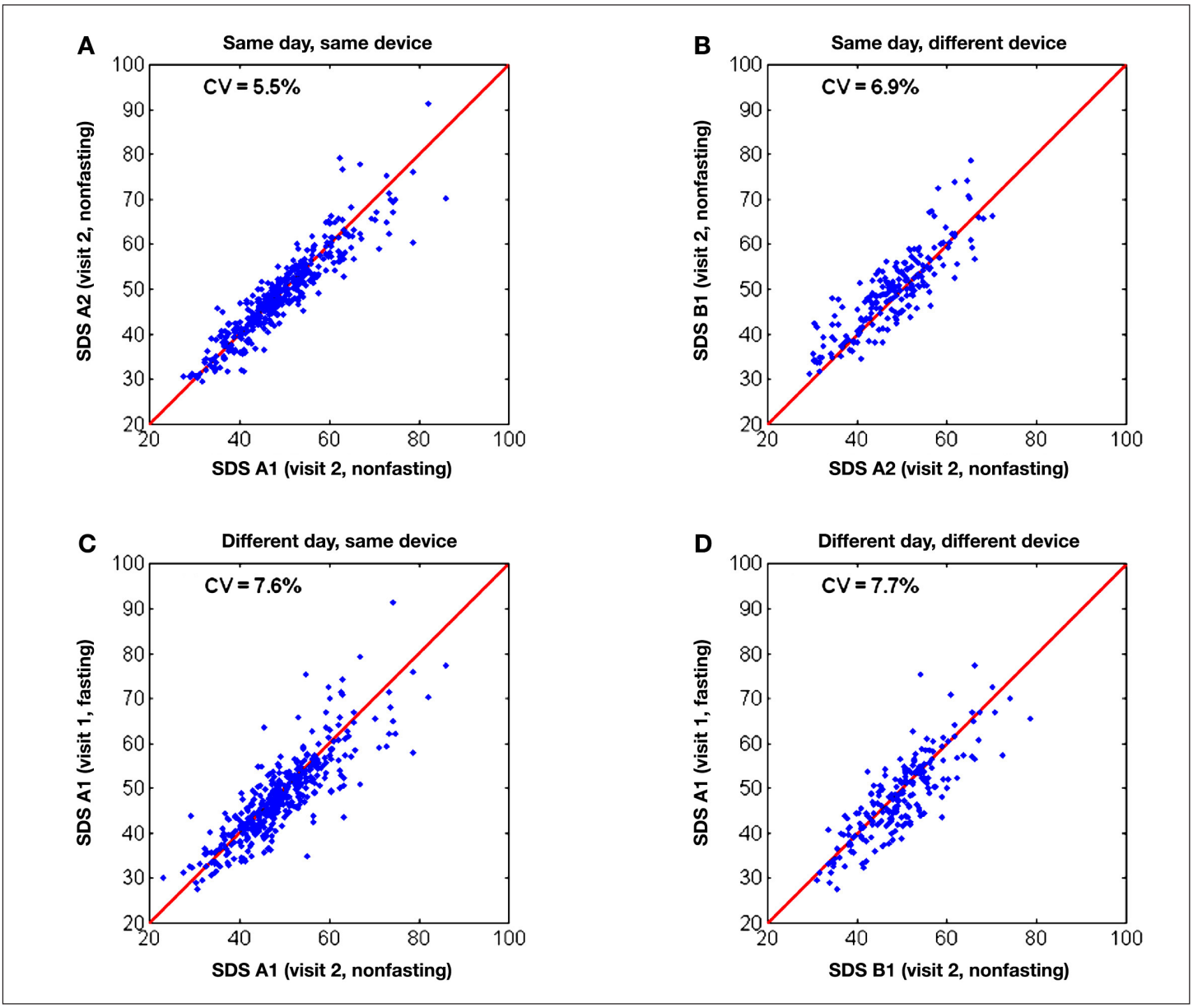

Figure 5. Paired test–retest SDS values.

There are fewer points in panel B than in panel A because centers did not receive the second SFS instrument until midway through the study. Panel C reflects SFS measurements collected on different days (visit 1, fasting, versus visit 2, nonfasting) on a common instrument (device A; Hoorn CV = 7.6%). Pairs in panel D correspond to measurements collected on different days (visit 1, fasting, versus visit 2, nonfasting) with different SFS instruments (device A versus device B; Hoorn CV = 7.7%). The CVs shown in **Figure 5** are comparable to that of the interday CV of the FPG test, which was found to be 6.7% in the Hoorn study[21] and 8.1% in the ENGINE study.[22] In both of these studies, FPG samples were processed with a common instrument/analyzer.

Figure 6 presents the results of SFS measurements collected on the same day (visit 1, fasting) on a common instrument (device A) but with the first measurement collected in a fasting state and the second measurement collected 1 h after ingesting a 75 g glucose challenge (Hoorn CV = 5.7%).

Although 11.1% of study completers were unable to obtain a valid SFS measurement on their first measurement attempt (SFS $A1_{nonfast}$), when a second measurement attempt (SFS $A2_{nonfast}$) was allowed, the fraction of subjects without a valid measurement decreased to 2.7%. When allowing a second measurement attempt, the SFS AUC and pAUC were 0.675 and 0.180, respectively, and were not significantly different from the single-attempt results.

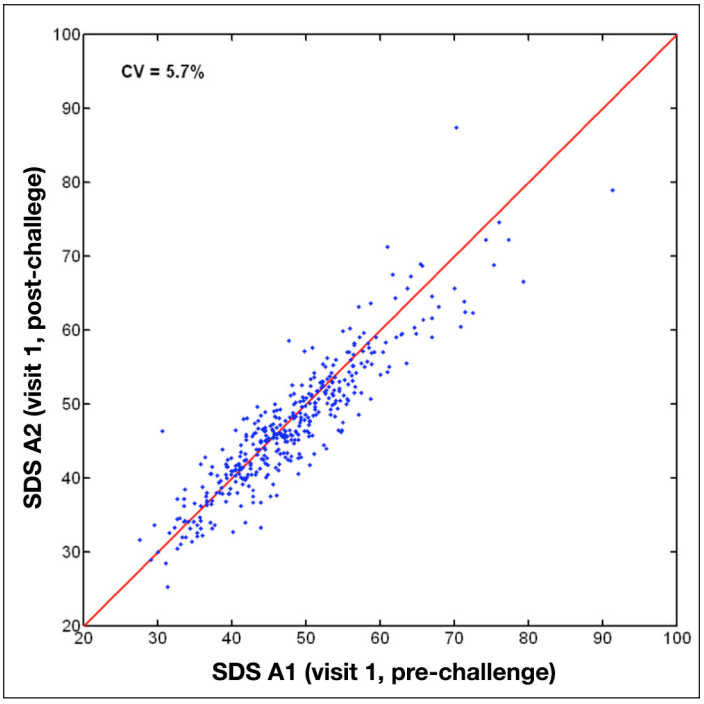

Figure 6. Pre- versus post-glucose challenge SDS values.

Discussion

In this study, when screening for AGT, the ROC curve of SFS was comparable to that of A1C and superior to that of FPG for $0.2 \leq FPR \leq 0.5$. A literature review determined that the FPR of the FPG test for detecting AGT in large cohorts of at-risk, previously undiagnosed subjects was constrained to this range.[15–18] The sensitivity and FPR of SFS at a test threshold of 50 U were most comparable to that of A1C at a threshold of 5.7%.

The interday, intradevice Hoorn CV for SFS (7.6%) was comparable to that of the FPG test (6.7–8.1%).[21,22] The use of different SFS devices for repeat testing did not significantly elevate the interday CV (7.7% versus 7.6%). The Hoorn CV for nonfasting SFS measurements made on a common device on the same day was 5.5%, which is comparable to the Hoorn CV for pre- versus post-glucose challenge SFS measurements of fasting subjects (5.7%).

The tradeoff between a test's sensitivity and FPR is described by its ROC curve. As seen in **Figure 4**/**Table 2**, SFS exhibited the highest AGT sensitivity (68.2%) of all screening tests involved in the NSEEDS trial. The FPR of SFS was 37.7%, which was slightly higher than that of the A1C test (30.7%) at the ADA-recommended screening threshold of 5.7%.[3] The FPR of the FPG test was lower (19.3% at the ADA-recommended threshold of 100 mg/dl), but at the cost of decreased AGT sensitivity (51.8%).

While detection of undiagnosed frank diabetes is a critical aspect of primary screening,[23–25] screening strategies that are also effective in detection of AGT are most desirable, because impaired glucose tolerance (IGT) is known to be an important early indicator of disease that can lead to overt complications without intervention. Work by Tominaga and coauthors[26] has demonstrated that the hazard ratio for death from cardiovascular disease is significantly elevated in those with IGT versus NGT (ratio = 2.2). These researchers found no significant increase in the hazard ratio for individuals with impaired versus normal fasting glucose.[26] Other investigators have established a strong association

between cardiovascular complications and compromised glucose tolerance,[27,28] and primary prevention studies such as the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study and the Diabetes Prevention Study have focused on IGT as the most reliable early indicator of glycemic dysfunction in type 2 diabetes.[29–31] It is therefore desirable that a primary screening test be as sensitive as possible in identifying individuals with AGT.

Maximizing AGT sensitivity by choosing a moderate FPR is justified if ruling out disease in false positive cases is not excessively inconvenient and/or costly relative to the benefits of early detection and intervention. In a modeling study, Chatterjee and coauthors[32] found that widespread opportunistic screening for type 2 diabetes was economically superior to the case of no or limited screening, after accounting for the costs of screening and therapeutic intervention, even for moderate FPRs. The Diabetes Prevention Program Research Group[33] found that widespread opportunistic screening and implementation of Diabetes Prevention Program interventions were cost-effective or marginally cost-saving, even if metformin therapy was extended to individuals as old as 65 years of age.

While the need for effective primary screening methods is well established, multiple obstacles limit the effectiveness of existing blood-based screening modalities. Patient convenience and compliance are barriers to the effectiveness of FPG and OGTT, which require overnight fasting.[2,4] As shown earlier, FPG suffers from poor sensitivity at its typical screening thresholds. Alternative risk scores that are derived from questionnaire-based risk factor inventories may translate to decreased motivation on the part of the patient to continue testing or to initiate lifestyle interventions.[34]

Limitations include that the study was not powered to do subgroup analyses based on skin tone or ethnicity. Also, FPG samples were not collected on multiple study days to allow for a comparison of the CVs of SFS and FPG on the same population. A strength of the study is that all members of the study cohort were at risk for type 2 diabetes per ADA guidelines and therefore represent the target population for diabetes screening. In addition, head-to-head SFS, FPG, A1C, and OGTT data were acquired from all patients in the analysis set. The cohort also had a representative mixture of patient age, gender, ethnicity, and BMI.

Conclusions

In the NSEEDS trial, SFS was as accurate as FPG and A1C for detection of AGT ($0.2 \leq FPR \leq 0.5$), and the AGT sensitivity and specificity of SFS at the recommended decision threshold (SDS = 50) were equivalent to A1C at a decision threshold of 5.7%. Larger trials are needed to definitively understand the performance of SFS for detection of AGT in a multiethnic population at risk for prediabetes and type 2 diabetes.

Elimination of overnight fasting, the absence of blood, and real-time communication of screening results are significant advantages of SFS relative to conventional blood-based measurements. Skin fluorescence spectroscopy has potential to facilitate widespread opportunistic screening of individuals at risk for type 2 diabetes.

Funding:

This study was sponsored by VeraLight Inc.

Disclosures:

The authors are former employees of VeraLight Inc.

Acknowledgments:

The principal investigators and research centers for the NSEEDS trial were Michael L. Kyle, M.D. (Radiant Research, Chicago, IL); Tami Helmer, M.D. (Radiant Research, Minneapolis, MN); Michael J. Noss, M.D. (Radiant Research, Cincinnati, OH); William Patrick Jennings, M.D. (Radiant Research, San Antonio, TX); Daniel H. Brune, M.D. (Accelovance, Peoria, IL); Martin L. Kabongo, M.D. (Accelovance, San Diego, CA); Earl F. Martin, M.D. (Dynamed Clinical Research, Tomball, TX); Audrey Lacour, M.D. (JUNO Research LLC, Houston, TX); David Bolshoun, M.D. (Radiant Research, Denver, CO). The authors thank Jeff Way who oversaw all training and data collection at the clinical centers.

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