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

ORIGINAL ARTICLE

Noninvasive Skin Fluorescence Spectroscopy for Diabetes Screening

Alin Stirban, MD, PhD

Abstract

The development of cost-effective, simple, and reproducible tests for diabetes screening represents a priority of modern medicine in light of the increasing prevalence of diabetes mellitus. Besides fasting plasma glucose, the oral glucose tolerance test, and glycated hemoglobin A1c, several tests have been proposed, among them the assessment of skin fluorescence spectroscopy (SFS). This article comments on the article by Olson and coauthors published in this issue of *Journal of Diabetes Science and Technology* and comprehensively reviews related available information. Overall, SFS seems to represent an easy-to-use, noninvasive tool that adds value to existing tests for diabetes screening.

J Diabetes Sci Technol 2013;7(4):1001–1004

In November 2012, the World Health Organization released some alarming data stating that there are 366 million people with diabetes worldwide, a number estimated to increase to 550 million by 2030. Around 50% of people with diabetes are undiagnosed, a problem that is higher in low- and middle-income countries, where 80% of people with diabetes live. Undiagnosed and untreated diabetes is a major cause of morbidity and mortality, and it is estimated that diabetes is responsible for 4.6 million deaths each year.[1] Therefore, besides efforts in treating and preventing diabetes, screening for diabetes is paramount. But why are we performing so poorly in diagnosing diabetes? Some of the reasons are related to the fact that tests are time-consuming [oral glucose tolerance test (OGTT)], need a complex laboratory setting and validation [glycated hemoglobin A1c (HbA1c)], or require prolonged fasting [fasting plasma glucose (FPG)].

Therefore, efforts have been made to develop noninvasive, fast, reproducible, and reliable tests for diabetes screening. Some of these methods rely on the assessment of skin fluorescence. A short theoretical background of this assessment is provided.

Advanced glycation end products (AGEs) result from the nonenzymatic reaction of reducing sugars with proteins, lipids, and nucleic acids.[2] The enhanced generation and accumulation of AGEs in diabetes have been linked to increased cardiovascular risk and the risk for development of diabetes complications.[2,3] Elevated levels of circulating AGEs are believed to play a major role in the pathogenesis of cardiovascular disease in diabetes[4–6] as well as in that of diabetes complications.[3,7] The Diabetes Control and Complications Trial showed that intensified glycemic control

Author Affiliation: Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany

Abbreviations: (AGE) advanced glycation end product, (CV) coefficient of variation, (FPG) fasting plasma glucose, (HbA1c) glycated hemoglobin A1c, (IGT) impaired glucose tolerance, (OGTT) oral glucose tolerance test, (SFS) skin fluorescence spectroscopy, (T2DM) type 2 diabetes mellitus

Keywords: advanced glycation endproducts, skin fluorescence spectroscopy, diabetes, screening

Corresponding Author: Alin Stirban, M.D., Ph.D., Profil Institut für Stoffwechselforschung GmbH, Hellersbergstraße 9, D-41460 Neuss, Germany; email address alin.stirban@profil.com

results in a decrease in microvascular complication,[8] an effect that lasts for years.[9] This latter aspect was attributed to the so-called "metabolic memory."[9] Advanced glycation end products accumulate within organs that are affected by diabetes complications and have a long persistence within the body,[10] thus representing an excellent candidate for mediating the metabolic memory. Because AGEs increase early in the course of diabetes,[11] they might be also used for diabetes diagnosis.

A simple, noninvasive method was made available allowing for the measurement of skin fluorescence [skin fluorescence spectroscopy (SFS)], a parameter that mirrors skin AGE accumulation.[12] Skin fluorescence spectroscopy was validated against biochemical analyses of AGEs in dermal tissue in arm biopsies.[12,13] Even though SFS measures not only fluorescent AGEs, but also redox-regulated fluorophores such as NADH, flavin adenine dinucleotide, porphyrines, and nonglycated substances,[14,15] AGEs-linked fluorescence seems to play a major role. Thus, 76% of SFS variability can be explained by pentosidine variability, a major fluorescence-exerting AGE.[13] Therefore, assessment of SFS can be regarded as a surrogate parameter for skin AGEs accumulation.

Several methods for noninvasive assessment of tissue fluorescence spectroscopy are available for measurements of the skin (AGE Reader, DiagnOptics, Groningen, the Netherlands, or SCOUT DS, VeraLight, Albuquerque, NM), the cornea, or the eye lens (Fluorotron, OcuMetrics, San Jose, CA). These methods allow for a fast, reproducible, and cost-effective measurement of AGEs accumulation.[12,16,17]

In this issue of *Journal of Diabetes Science and Technology*, Olson and coauthors[18] present data from an elegant multicenter study performed at nine U.S. centers. The main scope of the article was to evaluate the diagnostic value of SFS, FPG, and HbA1c versus a 75 g OGTT for the diagnosis of abnormal glucose tolerance (defined as a venous plasma glucose ≥140 mg/dl 2 h following an OGTT) in a population of 479 previously undiagnosed subjects at risk for developing type 2 diabetes mellitus (T2DM). Secondary objectives were SFS reproducibility, as well as the influence of fasting status on SFS measurements. Skin fluorescence spectra were collected and analyzed with SCOUT DS devices.

The first and main message of Olson and coauthors[18] is that, for abnormal glucose tolerance screening, the SFS has similar performance to FPG and HbA1c. The sensitivity for SFS was 68.2% (at a threshold of 50 on the SCOUT diabetes score scale), 64.5% for HbA1c (threshold 5.7%), and 51.8% for FPG (threshold 100 mg/dl); the corresponding false positive rate of the tests were 37.7%, 30.7%, and 19.3%, respectively.

These data are in line with previous data by Maynard and coauthors[19] showing in subjects with T2DM that SFS (SCOUT DS) has a superior sensitivity to FPG and HbA1c for detection of impaired glucose tolerance (IGT). At a comparable specificity, the sensitivity for detecting IGT was 58.0% for FPG, 63.8% for HbA1c, and 74.7% for SFS.

Further data by Tentolouris and coauthors[20] in a group of 398 persons at risk for developing T2DM add to this evidence. Dysglycemia [≥5.7% (39 mmol/mol)] or diabetes [≥6.5% (47.5 mmol/mol)] were diagnosed using HbA1c measurements. Random capillary glucose measurements, the American Diabetes Association Diabetes Risk Test, as well as the SFS (SCOUT DS) were comparators. Skin fluorescence spectroscopy was superior to random capillary glucose testing or the Diabetes Risk Test for recognizing dysglycemia or diabetes.

In a further study, measurements of the eye lens SFS (Fluorotron) contributed to the diagnosis of T2DM with a sensitivity of 79% and a specificity of 100%.[21]

In a study performed in 218 persons with intermediate diabetes risk, Smit and coauthors[22] compared SFS and an SFS-based decision tree with FPG, HbA1c, and additionally with the FINDRISC questionnaire ± FPG for detection of IGT and diabetes. The authors concluded that the SFS-based decision tree is superior to FPG and noninferior to HbA1c in detecting diabetes/IGT in this population.

The second important message of the article by Olson and coauthors[18] is the good reproducibility of SFS measurements for within-day testing, between-day testing, and testing with different devices. Reproducibility was expressed as

the coefficient of variation (CV) calculated in accordance with the Hoorn study.[23] For measurements performed with the same device within one day, the intrasubject CV was 5.5%; the intraday, interdevice CV was 6.9%. The CV for measurements performed with the same device on different days was 7.6% and was 7.7% using different devices on different days.

In line with this, we found (using the AGE Reader) that the intraindividual variability of fasting SFS within 6 weeks was 6.9% and within 12 weeks 10.9%.[24]

In one of the first validation studies for SFS (AGE Reader), an intraindividual variation of 5.03% was reported for measurements performed within one day, as well as an intraseasonal variation of 5.87%.[12] Another study group reported an intraindividual variation for SFS (AGE Reader) of 4.9% when four consecutive measurements were done within one day.[25]

The third important message of Olson and coauthors[18] is that measurements are not majorly influenced by the fasting status. When comparing measurements performed in fasting state with measurements performed on another day in non-fasting state, the CV was 7.6%. The CV for fasting subjects pre-glucose challenge versus post-glucose challenge SFS measurements (1 h following the OGTT) was 5.7%, comparable to the CV for two nonfasting SFS measurements made on a common device on the same day that accounted for 5.5%.

A small postprandial increase in SFS has been described in some pilot studies[26,27] but not in all.[25] Studies showing a postprandial increase in SFS (AGE Reader) reported postprandial changes of 11.6% in subjects with T2DM and of 8.7% in healthy subjects at 2 h following a high-fat meal[26] and of 9% at 3 h but no increase at 1 and 2 h following an OGTT in healthy volunteers.[27] We have recently shown in people with T2DM, that a cooked, mixed test meal accounted for a nonsignificant postprandial increase of 3.6% in SFS.[24]

Even though there might be a contribution of meal composition on postprandial SFS variation, this seems to be of small magnitude, and therefore, for screening purposes, the measurement of SFS does not necessarily require fasting.

Overall, the reproducibility of SFS measurements seems to be robust (for both devices, SCOUT DS and AGE Reader), and in addition to the study by Olson and coauthors,[18] several studies have shown the utility of SFS measurements for diabetes screening.[19–22] Moreover, SFS measurements provide additional information to the UK Prospective Diabetes Study risk score in people with T2DM,[28] correlate with the severity of peripheral and autonomic diabetic neuropathy,[29] and can be used for the identification of subjects with T2DM and an increased risk for developing microvascular[30] and macrovascular complications.[31]

Therefore, the measurement of SFS seems to be of interest for the diagnosis of diabetes, the assessment of cardiovascular risk, as well as the risk for developing diabetes complications.

References:

1. Partnership for Maternal, Newborn, and Child Health; World Health Organization. November 14 is World Diabetes Day! http://www.who.int/pmnch/media/news/2012/20121114_worlddiabetesday/en/.
2. Peppa M, Uribarri J, Vlassara H. Advanced glycoxidation. A new risk factor for cardiovascular disease? Cardiovasc Toxicol. 2002;2(4):275–87.
3. Ahmed N, Thornalley PJ. Advanced glycation endproducts: what is their relevance to diabetic complications? Diabetes Obes Metab. 2007;9(3):233–45.
4. Nin JW, Jorsal A, Ferreira I, Schalkwijk CG, Prins MH, Parving HH, Tarnow L, Rossing P, Stehouwer CD. Higher plasma levels of advanced glycation end products are associated with incident cardiovascular disease and all-cause mortality in type 1 diabetes: a 12-year follow-up study. Diabetes Care. 2011;34(2):442–7.
5. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414(6865):813–20.

6. Tan KC, Chow WS, Ai VH, Metz C, Bucala R, Lam KS. Advanced glycation end products and endothelial dysfunction in type 2 diabetes. Diabetes Care. 2002;25(6):1055–9.
7. Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. N Engl J Med. 1988;318(20):1315–21.
8. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.
9. Pop-Busui R, Herman WH, Feldman EL, Low PA, Martin CL, Cleary PA, Waberski BH, Lachin JM, Albers JW; DCCT/EDIC Research Group. DCCT and EDIC studies in type 1 diabetes: lessons for diabetic neuropathy regarding metabolic memory and natural history. Curr Diab Rep. 2010;10(4):276–82.
10. Vlassara H, Bucala R, Striker L: Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. Lab Invest. 1994;70(2):138–51.
11. Gradinaru D, Borsa C, Ionescu C, Margina D: Advanced oxidative and glycoxidative protein damage markers in the elderly with type 2 diabetes. J Proteomics. 2013. Epub ahead of print.
12. Meerwaldt R, Graaff R, Oomen PH, Links TP, Jager JJ, Alderson NL, Thorpe SR, Baynes JW, Gans RO, Smit AJ: Simple non-invasive assessment of advanced glycation endproduct accumulation. Diabetologia. 2004;47(7):1324–30.
13. Smit AJ, Gerrits EG. Skin autofluorescence as a measure of advanced glycation endproduct deposition: a novel risk marker in chronic kidney disease. Curr Opin Nephrol Hypertens. 2010;19(6):527–33.
14. Na R, Stender IM, Ma L, Wulf HC. Autofluorescence spectrum of skin: component bands and body site variations. Skin Res Technol. 2000;6(3):112–117.
15. Sell DR, Nemet I, Monnier VM: Partial characterization of the molecular nature of collagen-linked fluorescence: role of diabetes and end-stage renal disease. Arch Biochem Biophys. 2010;493(2):192–206.
16. Conway BN, Aroda VR, Maynard JD, Matter N, Fernandez S, Ratner RE, Orchard TJ. Skin intrinsic fluorescence is associated with coronary artery disease in individuals with long duration of type 1 diabetes. Diabetes Care. 2012;35(11):2331–6.
17. Kessel L, Hougaard JL, Sander B, Kyvik KO, Sorensen TI, Larsen M. Lens ageing as an indicator of tissue damage associated with smoking and non-enzymatic glycation--a twin study. Diabetologia. 2002;45(10):1457–62.
18. Olson BP, Matter NI, Ediger MN, Hull EL, Maynard JD. Noninvasive skin fluorescence spectroscopy is comparable to hemoglobin A1c and fasting plasma glucose for detection of abnormal glucose tolerance. J Diabetes Sci Technol. 2013;7(4):990–1000.
19. Maynard JD, Rohrscheib M, Way JF, Nguyen CM, Ediger MN. Noninvasive type 2 diabetes screening: superior sensitivity to fasting plasma glucose and A1C. Diabetes Care. 2007;30(5):1120–4.
20. Tentolouris N, Lathouris P, Lontou S, Tzemos K, Maynard J: Screening for HbA1c-defined prediabetes and diabetes in an at-risk greek population: Performance comparison of random capillary glucose, the ADA diabetes risk test and skin fluorescence spectroscopy. Diabetes Res Clin Pract. 2013;100(1):39–45.
21. Koefoed Theil P, Hansen T, Larsen M, Pedersen O, Lund-Andersen H. Lens autofluorescence is increased in newly diagnosed patients with NIDDM. Diabetologia. 1996;39(12):1524–7.
22. Smit AJ, Smit JM, Botterblom GJ, Mulder DJ. Skin autofluorescence based decision tree in detection of impaired glucose tolerance and diabetes. PLOS ONE. 2013. Forthcoming.
23. Mooy JM, Grootenhuis PA, de Vries H, Kostense PJ, Popp-Snijders C, Bouter LM, Heine RJ. Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. Diabetologia. 1996;39(3):298–305.
24. Stirban A, Pop A, Fischer A, Heckermann S, Tschoepe D. Variability of skin autofluorescence measurement over 6 and 12 weeks and the influence of benfotiamine treatment. Diabetes Technol Ther. 2013. To be published.
25. De Ranitz-Greven WL, Kaasenbrood L, Poucki WK, Hamerling J, Bos DC, Visser GH, Biesma DH, Beulens JW, de Valk HW. Advanced glycation end products, measured as skin autofluorescence, during normal pregnancy and pregnancy complicated by diabetes mellitus. Diabetes Technol Ther. 2012;14(12):1134–9.
26. Stirban A, Nandrean S, Negrean M, Koschinsky T, Tschoepe D. Skin autofluorescence increases postprandially in human subjects. Diabetes Technol Ther. 2008;10(3):200–5.
27. Noordzij MJ, Lefrandt JD, Graaff R, Smit AJ. Skin autofluorescence and glycemic variability. Diabetes Technol Ther. 2010;12(7):581–5.
28. Lutgers HL, Gerrits EG, Graaff R, Links TP, Sluiter WJ, Gans RO, Bilo HJ, Smit AJ: Skin autofluorescence provides additional information to the UK Prospective Diabetes Study (UKPDS) risk score for the estimation of cardiovascular prognosis in type 2 diabetes mellitus. Diabetologia. 2009;52(5):789–97.
29. Meerwaldt R, Links TP, Graaff R, Hoogenberg K, Lefrandt JD, Baynes JW, Gans RO, Smit AJ. Increased accumulation of skin advanced glycation end-products precedes and correlates with clinical manifestation of diabetic neuropathy. Diabetologia. 2005;48(8):1637–44.
30. Gerrits EG, Lutgers HL, Kleefstra N, Graaff R, Groenier KH, Smit AJ, Gans RO, Bilo HJ. Skin autofluorescence: a tool to identify type 2 diabetic patients at risk for developing microvascular complications. Diabetes Care. 2008;31(3):517–21.
31. Lutgers HL, Graaff R, Links TP, Ubink-Veltmaat LJ, Bilo HJ, Gans RO, Smit AJ. Skin autofluorescence as a noninvasive marker of vascular damage in patients with type 2 diabetes. Diabetes Care. 2006;29(12):2654–9.