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Skin Autofluorescence and Glycemic Variability

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Abstract

Background: Accumulation of advanced glycation end products (AGEs) is accelerated during glycemic and oxidative stress and is an important predictor of complications in diabetes mellitus (DM).

Study Design: Here we both review and present original data on the relationship between skin autofluorescence (SAF), a noninvasive measure of AGEs, and short- and intermediate-term glycemic variations.

Results: Acute changes in glucose levels during an oral glucose tolerance test in 56 persons with varying degrees of glucose tolerance did not influence SAF. AGE-rich meals result in a transient postprandial rise in SAF of 10% 2–4 h later. This could not be attributed to meal-induced glycemic changes and is probably caused by the AGE content of the meal. In type 1 DM major intermediate-term improvements of glycemic control as depicted by multiple hemoglobin A1c (HbA1c) measurements were associated with lower skin AGE levels. In a well-controlled, stable type 2 DM cohort, only a weak correlation was found between SAF and HbA1c. In both studies skin AGE/SAF levels predicted complications of diabetes with an accuracy superior to that of HbA1c. SAF has also been proposed as a new tool in diagnosing impaired glucose tolerance (IGT) and DM. It proved to be more sensitive than either fasting glucose or HbA1c.

Conclusions: SAF is not influenced by short-term glycemic variations. AGE-rich meals may, however, cause a transient rise postprandially. There is a weak correlation between SAF or skin AGEs and current or time-integrated HbA1c levels. SAF has strong added value in risk prediction of complications of diabetes and is a promising tool for early detection of diabetes and IGT.

Introduction

ADVANCED GLYCATION END PRODUCTS (AGEs) play a major pathogenetic role in many age-related diseases.¹ Especially in diabetes mellitus (DM) and renal failure, AGE accumulation is accelerated and causes long-term complications and increased mortality.^{2–6} Tissue and cellular damage as a result of AGEs results primarily from AGEs forming cross-links between proteins and from binding to and subsequent activation of cell membrane pro-inflammatory receptors, including the receptor for AGEs.⁷

Skin autofluorescence (SAF) has become a validated and widely accepted noninvasive method to assess tissue accumulation of AGEs.⁸ Not surprisingly, SAF proved to be a strong and independent predictor of complications in DM.² Also, it has prognostic value on top of the United Kingdom Prospective Diabetes Study (UKPDS) risk score in predicting mortality in type 2 diabetes.^{3,4}

AGEs, especially the accumulation in long-lived tissues like skin collagen, have been proposed by several groups including the UKPDS group as a carrier of long-term metabolic memory of glycemic and oxidative stress.⁹ Therefore, a

correlation between SAF as a measure of tissue AGEs and other parameters of glycemic control might be expected. In this article we review and present original data on the relationship among glucose levels, glycosylated hemoglobin A1c (HbA1c), and SAF.

SAF and Short-Term Glycemic Variability

We studied the effects of short-term glucose variations during a glucose tolerance test on SAF in 56 persons. Inclusion criteria were the presence of one or more risk factors for diabetes, namely, obesity or other criteria for the metabolic syndrome, physical inactivity, or an abnormal high glucose value or HbA1c in the past. Exclusion criteria were known diabetes, chronic kidney disease with a serum creatinine of $>120 \mu\text{mol/L}$, or an acute cardiovascular event in the previous 3 months.

Subjects underwent an oral glucose tolerance test (OGGT) of 75 g of glucose dissolved in 120 mL of water. Glucose, HbA1c, and SAF were determined at baseline. Furthermore, glucose and SAF were also measured 2 h after ingestion of the 75 g of glucose. After the OGGT, patients were classified as having normal glucose tolerance, prediabetes, and frank

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diabetes according to the 2003 American Diabetes Association criteria.¹⁰ Here, a normal glucose tolerance was defined as a fasting glucose level of <5.6 mmol/L and a glucose level of <7.8 mmol/L in the OGTT at 2 h. Prediabetes was defined as a fasting glucose level of 5.6–6.9 mmol/L or a glucose level of 7.8–11.0 mmol/L at 2 h in the OGTT. Diabetes was defined as a fasting glucose level of ≥ 7.0 mmol/L or a glucose level of >11.0 mmol/L at 2 h in the OGTT. Of the 56 subjects, 18 had a normal glucose tolerance, 25 had prediabetes, and 13 diabetes.

Baseline characteristics are shown in Table 1. No differences existed between the different groups concerning sex, age, body mass index, blood pressure, tobacco use, and serum creatinine. HbA1c at baseline was significantly different between the groups ($P < 0.001$) with a higher HbA1c in the prediabetes groups than in the normal glucose tolerance group, as could be expected.

Results concerning SAF are shown in Table 2. SAF at baseline appeared to be higher for impaired glucose tolerance (IGT) and diabetes than for normal glucose tolerance. SAF was 2.04 ± 0.55 arbitrary units (AU) for normal glucose tolerance, 2.27 ± 0.71 AU for IGT, and 2.54 ± 2.54 AU for diabetes. However, these differences were not statistically significant ($P = 0.18$), probably as a result of the small number of subjects. Using analysis of variance, the differences among the three glucose tolerance groups were evaluated. Glucose at baseline and at 2 h and also the increase in glucose were significantly different in the three glucose tolerance groups, with increasing glucose values from normal glucose tolerance to diabetes. No increase of SAF at 2 h after oral intake of 75 g of glucose was found compared to baseline, even though the glucose level rose significantly. SAF was 2.24 ± 0.74 AU while fasting and 2.22 ± 0.65 AU at 2 h. The changes in SAF were independent of baseline SAF and level of glucose tolerance or change in glucose levels.

In conclusion, SAF is not immediately influenced by a rise in serum glucose levels as measured during an OGTT.

The Influence of an AGE-Rich Meal on SAF

Food consumption may influence the accumulation of AGEs and thus SAF by several mechanisms. First of all, intake of food can result in glycemic stress, promoting the formation of AGEs, especially when consisting of fast-acting carbohydrates. Over prolonged periods this will enhance the tissue accumulation of AGEs. Second, food is an exogenous source

of AGEs, with broiled and fried food having markedly high AGE content.^{11,12} An AGE-rich meal might therefore influence the measurement of SAF, even when the short-acting glucose load has no effects on SAF, as discussed above. Stirban et al.¹³ investigated the effect of a 580 kCal meal reported to have an intermediate AGE content of 8,519 kU on SAF. Actually, both the caloric and AGE contents are substantial. In this study, SAF was measured in a fasting state, as well as 2 and 4 h postprandially, in 21 Caucasian subjects, of whom 10 were healthy and 11 had DM. A statistically significant increase of 10% in SAF was found 2 h postprandially, from 1.97 ± 0.62 AU to 2.17 ± 0.62 AU. In the diabetes subjects, SAF increased 11.6%, and glucose levels rose significantly from 7.55 to 8.55 mmol/L at 2 h. In healthy subjects, there was an 8.7% increase in SAF at 2 h, while glucose did not significantly rise (from 4.3 to 4.6 mmol/L). Individuals with diabetes had a slightly higher increase in SAF than the healthy individuals: 11.6% versus 8.7%. At 4 h SAF had still not returned to baseline levels: 2.16 ± 0.72 AU ($P < 0.01$). We did a similar study with a breakfast of two toasted slices of bread and cheese and 220 mL of caramelized pudding, which has an estimated AGE content of 2,700 kU. The AGE content was estimated by the same method as Stirban et al.¹³ by using lists with the specific AGE contents of different foods provided by Goldberg et al.¹¹ In nine healthy subjects (18–20 years old, with eight of the nine subjects female), the SAF was measured before and at 1, 2, and 3 h after the meal. At baseline SAF was 2.05 ± 0.32 AU. At 1 and 2 h no rise in SAF was observed, with an SAF of 2.00 ± 0.26 AU and 1.99 ± 0.34 AU, respectively. At 3 h postprandially, however, the SAF was 9% higher: 2.22 ± 0.27 AU ($P = 0.038$ in paired *t* test). Results of both studies are presented in Table 3.

In conclusion, meals rich in AGEs may result in a postprandial rise of SAF of maximally 10%. Considering the lack of effect of glucose, described above, the meal-induced rise in SAF is probably due to the AGE content of the food. We therefore recommend taking the possibility of such an increase into account when measurements of SAF are performed 2–4 h after an AGE-rich meal. The effects of meals with a normal to low AGE content are as yet unknown. For more information concerning the AGE content of different foods we refer to the available lists generated by Goldberg et al.¹¹ In general, unprocessed fruits, untoasted bread, and liquids like tea, coffee, and unheated milk do not contain a high amount of AGEs. Clearly, a fasting state would abolish all

TABLE 1. BASELINE CHARACTERISTICS IN THE TOTAL GROUP AND THE DIFFERENT GLUCOSE TOLERANCE SUBGROUPS

	Normal	Prediabetes	Diabetes	Total
<i>n</i>	18	25	13	56
Sex (male)	11	13	7	31
Age (years)	53.5 ± 10.5	56.8 ± 9.1	59.2 ± 18.4	56.3 ± 12.2
BMI (kg/m ²)	30.6 ± 6.3	30.8 ± 5.5	31.0 ± 5.7	30.8 ± 5.7
Blood pressure (mm Hg)				
Diastolic	86 ± 14	85 ± 13	83 ± 12	85 ± 13
Systolic	139 ± 16	140 ± 13	143 ± 25	140 ± 17
Current smoking	5	4	2	11
Creatinine (μ mol/L)	78.1 ± 26.3	82.7 ± 16.6	76.5 ± 21.1	79.7 ± 20.9
HbA1c (%)	5.5 ± 0.3	6.0 ± 0.3	6.2 ± 0.3	5.9 ± 0.4

Data are mean \pm SD values or number of patients. BMI, body mass index; HbA1c, hemoglobin A1c.

TABLE 2. RESULTS OF ORAL GLUCOSE TOLERANCE TEST ON GLUCOSE LEVEL AND SKIN AUTOFLUORESCENCE IN THE TOTAL GROUP AND IN THE DIFFERENT GLUCOSE TOLERANCE SUBGROUPS

	Normal	Prediabetes	Diabetes	Total	P value
Glucose (mmol/L)					
0h	5.1 ± 0.26	6.0 ± 0.46	6.93 ± 0.93	5.9 ± 0.87	<0.001
2h	5.34 ± 1.11	7.2 ± 1.92	11.2 ± 3.19	7.5 ± 3.0	<0.001
Δ	0.08 ± 1.21	1.19 ± 2.04	4.3 ± 3.6	1.56 ± 2.77	<0.001
SAF (AU)					
0h	2.04 ± 0.55	2.27 ± 0.71	2.54 ± 0.96	2.25 ± 0.74	0.18
2h	1.99 ± 0.54	2.28 ± 0.58	2.43 ± 0.90	2.22 ± 0.67	0.17
Δ	0.04 ± 1.65	0.01 ± 0.25	0.11 ± 0.18	0.033 ± 0.21	0.25

Differences among the three glucose tolerance groups were evaluated by analysis of variance and shown by the *P* value. AU, arbitrary units; SAF, skin autofluorescence.

potential influences from food consumption. If these meal-induced effects would be eliminated, the predictive value of SAF may even surpass the earlier reported values.

SAF and Intermediate-Term Glycemic Control Measured by HbA1c

While SAF represents a long-term memory of glycemic and oxidative stress, HbA1c represents a glycemic memory over a period of 3 months. HbA1c is considered an early glycation product or Amadori product. In monitoring glycemic control in diabetes patients, HbA1c is normally measured repeatedly over time. A correlation between HbA1c as an early glycation end product and SAF as a marker of tissue accumulation of AGEs can be expected. Several researchers indeed analyzed the relationship between HbA1c values over time and AGE accumulation in tissue measured either directly in skin biopsies or noninvasively as in SAF.^{14,15}

Gerrits et al.¹⁴ examined 452 patients with type 2 diabetes in a primary care setting who were well controlled (mean HbA1c, 7%). They found that after 3.3 years of follow-up the accumulation of AGEs in skin, measured as the rise in SAF at follow-up, had a weak but significant correlation with several integrated assessments of HbA1c (variance of HbA1c, mean HbA1c, maximum HbA1c, and HbA1c at baseline). Regression coefficients were <0.1; $P \leq 0.025$ (with addition of baseline SAF: overall adjusted $R^2 \sim 0.45$; $P < 0.001$).¹⁴ The major determinants of SAF at follow-up after 3 years were baseline SAF and age. Duration of diabetes and smoking were not correlated, and renal function was of marginal predictive value.

In a subpopulation of the Diabetes Control and Complications Trial, skin biopsy specimens of 216 patients with type 1 diabetes were examined for the presence of various

AGEs.^{15,16} The biopsies were performed near the end of the trial. Of these subjects, 122 had been treated with intensive treatment, and 94 had been treated conventionally during the previous 5 years. A strong positive relation among skin AGEs and age and duration of diabetes was found. Five years of intensive insulin therapy resulted in 24% lower HbA1c levels (7.1% in the intensive treatment group vs. 9.3% in the conventional treatment group). Moreover, AGEs measured in the skin biopsy samples were lower after intensive insulin treatment. In the intensive treatment group carboxymethyllysine (CML) and pentosidine were 9–13% and 9% lower, respectively, compared to the conventional treatment group. Cross-linking of skin collagen was lower in the intensive treatment group, resulting in 24% higher acid-soluble collagen and 50% higher pepsin-soluble collagen. The relationship between pentosidine and CML with different integrated HbA1c markers (mean HbA1c up to biopsy, mean HbA1c over the past year, HbA1c nearest to biopsy, and screening HbA1c) was assessed by performing univariate regression analysis. The relationship was again weak, but significant with $R^2 = 9.6\%$ and 13.8% for pentosidine and CML, respectively, for HbA1c nearest to biopsy and 8.9% and 16.1% , respectively, for mean HbA1c up to biopsy.

In conclusion, both Gerrits et al.¹⁴ and Monnier et al.¹⁵ found a weak relation between HbA1c and AGEs in skin measured either as SAF or directly in skin biopsies. Monnier et al.¹⁵ found HbA1c and skin AGE levels similarly lower in the group with 5 years of intensive treatment compared to the conventional treatment group. The better glycemic control no doubt resulted in a drop in glycemic stress and (to a lesser extent) oxidative stress.

The issue of predicting complications of diabetes by either HbA1c or AGEs measured in skin biopsies was also addressed by Monnier et al.¹⁵ and Genuth et al.¹⁶ Monnier et al.¹⁵

TABLE 3. RESULTS OF AN ADVANCED GLYCATION END PRODUCT-RICH MEAL ON SKIN AUTOFLUORESCENCE

	AGE content	n	SAF			P value
			0h	Postprandial	Δ	
Stirban et al. ¹³	8,518 kU	21	1.97 ± 0.62	2.17 ± 0.62	0.20	<0.01
Our results	2,700 kU	9	2.05 ± 0.32	2.22 ± 0.27	0.15	0.038

Skin autofluorescence (SAF) data are mean ± SD values. The statistical significance of the difference in SAF before and after the meal is shown by the *P* value. AGE, advanced glycation end product.

cross-sectionally found that all AGEs measured in the skin biopsy specimens were significantly associated with complications of diabetes like retinopathy, nephropathy, and neuropathy. After another 5 years of follow-up in this subpopulation of the Diabetes Control and Complications Trial, Genuth et al.¹⁶ found that the combination of furosine (glycated collagen) and the AGE CML predicted the risk of progression of retinopathy and nephropathy over the 10-year follow-up period. The predictive value of skin AGEs remained after adjustment for HbA1c. Moreover, the predictive value of HbA1c completely disappeared after correction for furosine and CML. They concluded that accumulation of AGEs in tissue appears to be a major contributor in the development of complications of diabetes and explains the phenomenon of metabolic memory. In another study, Lutgers et al.¹⁷ found that AGEs noninvasively measured as SAF proved to have predictive value far surpassing the value of HbA1c as established by several studies.^{2-4,16} The SAF added information to the classical UKPDS risk score in which HbA1c, duration of diabetes, and the classical risk factors for atherosclerosis are included.⁴

Value of SAF Compared to Fasting Glucose and HbA1c in Diagnosing DM and IGT

Maynard et al.¹⁸ evaluated the value of SAF in detecting undiagnosed DM or IGT in a naive population. They used an OGTT as the golden standard. A 2-h OGTT of >7.8 mmol/L was used to define IGT and values of >11.1 mmol/L defined DM following the 2003 American Diabetes Association criteria.¹⁰ From a total of 351 participants, IGT was found in 55 subjects and diabetes in 29 subjects. A fasting glucose of >5.5 mmol/L had a sensitivity of 58% and a specificity of 77%. The authors chose to examine the sensitivity of HbA1c and SAF at this particular specificity of 77%. At the specificity of 77%, HbA1c of 5.8 mmol/L did better with a sensitivity of 64%. SAF, however, was superior to both fasting glucose and HbA1c with a sensitivity of 75%, which was a statistically significant improvement over blood tests ($P < 0.05$). SAF, therefore, diagnosed 29% more subjects with abnormal glucose tolerance than fasting glucose and 17% more than HbA1c. The authors concluded that the use of SAF might prove a powerful tool for early detection of abnormal glucose regulation and prevention of resulting damage.

Preliminary, as yet unpublished results in a group of 57 subjects at risk for IGT or diabetes confirmed the superiority of SAF above fasting glucose and HbA1c in classifying subjects in categories of normal glucose tolerance versus IGT and diabetes. Using SAF as part of a simple decision tree led to misclassification of four out of 57 persons, while a fasting glucose >6 mmol/L would have led to misclassification of 17 subjects and using HbA1c values of >6% to misclassification of 14 subjects. Validation studies in other and larger cohorts are ongoing (A.J.S., preliminary results presented at the 2009 Advanced Technologies and Treatments for Diabetes conference, Athens, Greece).

Conclusions

SAF is not significantly influenced by short-term glycemic variations as measured during an OGTT. An AGE-rich meal may result in a postprandial rise after 2–4 h in SAF of maximally 10%. Intermediate-term glycemic variations as

measured by multiple HbA1c measurements (over time) are weakly related to SAF in both type 1 and type 2 DM, but dramatic improvements in HbA1c over years may be associated with a lower level of AGE in skin. Moreover, skin AGE and SAF are strong predictors of complications of diabetes and mortality with an accuracy far exceeding that of HbA1c and even that of most constituents of the UKPDS risk engine. SAF is also a promising tool in diagnosing IGT and DM and proved to be more sensitive than either fasting glucose or HbA1c.

Author Disclosure Statement

A.J.S. and R.G. are founders and stockholders of DiagonOptics B.V., The Netherlands, manufacturer of the AGE-Reader, which has been used as the device for performing skin autofluorescence measurements discussed in this study. M.J.N. and J.D.L. declare no competing financial interests.

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