

Advanced Glycation End Products, Measured as Skin Autofluorescence and Diabetes Complications: A Systematic Review

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Abstract

Background: Advanced glycation end products (AGEs) are long-lived tissue proteins that accumulate in diabetes. Skin AGEs measured in biopsy specimens strongly correlated with complications of diabetes. AGEs can also be measured noninvasively by the AGE Reader™ (DiagnOptics B.V., Groningen, The Netherlands). The aim of this review was to systematically review all articles on the association between skin autofluorescence (SAF), measured by the AGE Reader, and complications of diabetes.

Methods: We screened PubMed for studies on SAF and complications in diabetes mellitus type 1 and type 2. Seven articles met the inclusion criteria.

Results: All studies showed positive associations of SAF with one or more complications (all-cause mortality, cardiovascular mortality, micro- and macrovascular complications, neuropathy, and nephropathy), except retinopathy. Only three studies were of prospective design, with a follow-up of 3–5 years; the other four studies were cross-sectional. Studies were of large clinical heterogeneity.

Conclusions: This systematic review of literature showed an association of SAF with end-organ complications in diabetes, except retinopathy, in all seven studies. However, studies were of large clinical heterogeneity, only three studies had a prospective design, and five studies were from the same research group. More prospective studies, with a longer period of follow-up, larger group size, and strict definitions of complications and end points, are needed to demonstrate the potential role and benefit in clinical management before the widespread use of the AGE Reader can be recommended.

Introduction

THE INCIDENCE AND PREVALENCE of diabetes are increasing.^{1–3} Patients with diabetes can develop microvascular complications, such as retinopathy, nephropathy, and neuropathy, and macrovascular complications, including coronary heart disease and cerebrovascular accidents. Many risk factors are known, but all factors together cannot fully explain the risk of diabetes complications. This suggests that other pathophysiological mechanisms are operative. Increased tissue advanced glycation end products (AGEs) may well be such an alternative mechanism.

AGEs are permanently deposited glyco-oxidation products that are formed by different pathways. One is the Maillard reaction, in which glycated proteins are formed by a series of sequential reactions between glucose and proteins;⁴ the other is formation by reactive carbonyl compounds, which may form rapidly under oxidative stress.⁵ AGE formation and accumulation can cause damage by two pathways. First,

AGEs can form cross-links with proteins that affect the three-dimensional structure and thereby the functions of these proteins.⁶ Second, AGEs can cause harmful effects by the activation of receptors for AGEs. For instance, stimulation of the receptor for AGEs can lead to activation of second messengers and transcription factors that up-regulate harmful cytokines.⁷

AGEs accumulate in the body during aging.⁸ This process of accumulation is accelerated in several conditions with glycemic and oxidative stress, resulting in higher AGE levels in, for instance, patients with diabetes mellitus, renal failure, patients admitted to the intensive care unit, and patients who smoke.^{8–11} AGEs are cleared by the kidney; renal failure results in decreased clearance and thereby AGE accumulation.¹² AGEs, measured in skin biopsy specimens, are positively associated with the presence and severity of microvascular disease in patients with diabetes.^{13–15} In prospective studies in diabetes patients, the level of skin AGEs, measured in biopsy specimens, predicts the progression of microvascular complications (retinopathy and nephropathy), and the level of

serum AGEs predicts mortality rate (all-cause and cardiovascular).^{16,17} However, all these studies use invasive methods to measure AGEs, limiting clinical implementation of assessing AGE accumulation.

The level of AGEs in the skin can also be measured noninvasively by the AGE Reader™ (DiagnOptics B.V., Groningen, The Netherlands), formerly known as the AFR (Autofluorescence Reader).¹⁸ This noninvasive method uses skin autofluorescence (SAF) and is based on the specific fluorescence characteristics of some AGEs. SAF is validated against AGE levels in skin biopsy specimens (both fluorescent and nonfluorescent AGEs) in healthy controls, patients with diabetes, and patients on hemodialysis.^{19,20} Because the AGE Reader allows noninvasive estimations of skin AGEs, this method could be of clinical potential to predict diabetes complications and indeed can be purchased for this purpose. However, a systematic review on the current literature investigating the association of SAF, measured by the AGE Reader, with diabetes complications is lacking. Therefore we performed this systematic review to critically assess the current evidence for the potential of the AGE Reader to be used as a tool in daily clinical practice.

Subjects and Methods

Literature search

A literature search was carried out in PubMed to identify all relevant studies up to June 2010 regarding the association of skin AGEs, measured noninvasively by the AGE Reader or AFR, and complications in patients with diabetes mellitus. We used the search terms as mentioned in Table 1; search terms within the columns were connected with “or,” and finally the

columns were connected with “and” to yield our final search. Only original articles in English were included. Studies on the same topic in the reference lists of the reviewed articles were also retrieved.

Inclusion criteria

Any study that met the following criteria was included in this review:

- patients with diabetes mellitus type 1 or type 2
- SAF levels measured by the AGE Reader or AFR
- information concerning complications of diabetes

Outcomes of interest

The following subjects were classified as outcomes of interest:

- all-cause mortality
- cardiovascular mortality
- macrovascular complications
- microvascular complications
- separate microvascular complications
 - neuropathy
 - nephropathy
 - retinopathy

Statistics

Studies included a multitude of different patient groups and investigated different outcomes, as described in Table 2; therefore a meta-analysis could not be performed due to clinical heterogeneity.

All results and statistics in different studies are described in Table 3. The studies included used different statistics to describe outcome. Most cross-sectional studies described differences in SAF between patients with and without diabetes complications.^{22,23} One study used a β -coefficient.²¹ Two studies described a hazard ratio for developing complications,^{24,26} and two used odds ratios (ORs).^{25,27}

Different studies adjusted effects of SAF for different factors (Supplementary Table S1; Supplementary Data are available online at www.liebertonline.com/dia <<http://www.liebertonline.com/dia>>). Chabroux et al.²¹ adjusted for age, diabetes' duration, glycated hemoglobin (HbA1c), smoking, retinopathy, nephropathy, and neuropathy. Lutgers et al.²¹ adjusted only for age. Meerwaldt et al.²³ corrected for HbA1c, age, diabetes' duration, serum creatinine, and microalbuminuria in their analysis of the association of SAF with nerve conduction velocity. However, adjustments of differences in SAF between patients with and without neuropathy were not explicitly described. Monami et al.²⁴ adjusted for age and HbA1c. ORs mentioned in the follow-up study of Gerrits et al.²⁵ are adjusted for sex, body mass index, HbA1c, diabetes' duration, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking, and hypertension but not age. Results described by Meerwaldt et al.²⁷ are adjusted for age, body mass index, HbA1c, diabetes' duration, triglycerides, low-density lipoprotein cholesterol, smoking, hypertension, plasma creatinine, hemodialysis treatment, and coronary heart disease at baseline. Hazard ratios mentioned in the follow-up study of Lut-

TABLE 1. SEARCH STRATEGY

<i>Subjects</i>	<i>and</i>	<i>Method of measurement</i>	<i>and</i>	<i>Outcome</i>
Diabetes		skin advanced glycation endproducts		prediction
Mellitus		skin AGEs		predictive value
Diabetes		AGE-reader		complications
DM		AGE reader		cardiovascular complications
Diabetic patients		AFR		mortality
Diabetic subjects		autofluorescence reader		macrovascular complications
		skin autofluorescence		macrovascular complications
		autofluorescence		microvascular complications
		SAF		microvascular complications
				retinopathy
				nephropathy
				neuropathy

Search terms within the columns were connected with “or,” and the searches resulting from the columns were connected with “and” to yield our final search.

TABLE 2. STUDIES AND CHARACTERISTICS OF PARTICIPANTS

Study, country (year)	Design	Outcome	Number (n)	Mean \pm SD or mean (IQR)			Therapy	History of complications (% of diabetes patients)
				Age (years)	DM duration (years)	HbA1c (%)		
Chabroux et al., ²¹ France (2010)	Cross-sectional	Neuropathy, nephropathy, retinopathy	T1: 133 T2:— C:—	T1: 30 (23) T2:— C:—	T1: 17 (15) T2:—	T1: 8.0 (1.5) T2:—	100% insulin	41% microvascular disease: 9% neuropathy, 18% nephropathy, 40% retinopathy
Lutgers et al., ²² The Netherlands (2006)	Cross-sectional	Macrovascular, microvascular	T1:— T2: 973 C: 231	T1:— T2: 66 \pm 11 C: 52 \pm 17	T1:— T2: 4.2 (1.6–8.3)	T1:— T2: 7.0 \pm 1.3	16% insulin, 84% non-insulin treatment	39% macrovascular disease 49% microvascular disease: 28% neuropathy, 21% nephropathy, 20% retinopathy
Meerwaldt et al., ²³ The Netherlands (2005)	Cross-sectional	Neuropathic foot ulceration	T1 and T2 NP+ subjects: 24 T1 and T2 NP– subjects: 23 C: 21	57 \pm 12 53 \pm 13 58 \pm 10	17 \pm 12 13 \pm 10	8.2 \pm 1.09 7.6 \pm 0.85 5.9 \pm 0.72	75% insulin, 25% non-insulin treatment 83% insulin, 17% non-insulin treatment	17% coronary heart disease: 100% neuropathy, 88% retinopathy
Monami et al., ²⁴ Italy (2008)	Cross-sectional	Macrovascular (arteriopathy of the lower limbs, ischemic heart disease, stroke/TIA), neuropathy, foot ulceration, nephropathy, retinopathy	T1:— T2: 92 C:—	T1:— T2: 69.1 \pm 12.4 C:—	T1:— T2: 12.3 \pm 10.7 C:—	T1:— T2: 7.6 \pm 1.4 C:—	36% on insulin, 64% non-insulin treatment	Macrovascular disease: 28.3% ischemic heart disease, 14.1% stroke/TIA Microvascular disease: 30.4% neuropathy, 23.0% foot ulcers, 19.6% microalbuminuria, 8.7% retinopathy
Gerrits et al., ²⁵ The Netherlands (2008)	Prospective, follow-up 3.1 years	Microvascular (neuropathy, nephropathy, retinopathy)	T1:— T2: 881 C:—	T1:— T2: 66 \pm 11 C:—	T1:— T2: 4.0 (1.5–8.1)	T1:— T2: 6.6 (6.0–7.6)	15% insulin, 85% non-insulin treatment	37% macrovascular disease, 50% microvascular disease (24% neuropathy, 24% nephropathy, 19% retinopathy)
Lutgers et al., ²⁶ The Netherlands (2009)	Prospective, follow-up 3.1 years	All-cause mortality, cardiovascular events	T1:— T2: 967 C:—	T1:— T2: 66 \pm 11 C:—	T1:— T2: 4.2 (1.6–8.3) C:—	T1:— T2: 7.0 \pm 1.3 C: \pm	16% insulin, 84% non-insulin treatment	39% macrovascular disease, 53% microvascular disease (29% neuropathy, 25% nephropathy, 20% retinopathy)
Meerwaldt et al., ²⁷ The Netherlands (2007)	Prospective, follow-up 5 years	Cardiovascular mortality (prospective), coronary heart disease (cross-sectional)	T1: 48 T2: 69 C: 43	T1: 45 \pm 15 T2: 61 \pm 13 C: 53 \pm 16	T1: 20 \pm 11 T2: 10 (5–20)	T1: 7.9 \pm 1.0 T2: 8.2 \pm 0.9 C: 5.5 \pm 0.05	No information about insulin or oral therapy is given	T1: 27% coronary heart disease, 21% end-stage renal failure (on hemodialysis) T2: 45% coronary heart disease, 20% end-stage renal failure (on hemodialysis)

Number are expressed as mean \pm SD or median (interquartile range [IQR]).

C, control subjects without diabetes; DM, diabetes mellitus; HbA1c, glycated hemoglobin; NP+, diabetes patients with neuropathic foot ulceration, NP–, diabetes patients without clinical neuropathy; T1, DM type 1; T2, DM type 2; TIA, transient ischemic attack.

TABLE 3. RESULTS AND STATISTICS

Study, type (device)	Number	Statistical analysis, expressed as	Reference group	Mortality	Macrovascular complications	Microvascular complications	Neuropathy	Nephropathy	Retinopathy
Chabroux et al., ²¹ cross-sectional (AGE Reader)	T1: 133 T2:— Control:—	β -coefficient (95% CI)	T1 subjects without neuropathy T1 subjects without nephropathy T1 subjects without retinopathy				Neuropathy: 0.46 (0.02–0.91) ^a	Incipient nephropathy: 0.37 (0.03–0.70) ^b Overt or renal failure: 0.58 (0.18–0.99) ^b	<i>Moderate retinopathy:</i> 0.08 (–0.14 to 0.30) ^c <i>Severe retinopathy:</i> 0.12 (–0.17 to 0.42) ^c
Lutgers et al., ²² cross-sectional (AFR)	T1:— T2: 973 C: 231	Mean \pm SD SAF or mean SAF (95% CI)	T2 subjects without complications: 2.57 (2.50–2.65) Control: 2.14 \pm 0.6		T2 macrovascular complications: 2.91 (2.78–3.03) ^{*†} T2 micro- and macrovascular complications: 3.12 (3.01–3.23) ^{*†‡}	<i>T2 microvascular complications:</i> 2.71 (2.62–2.80) ^{*‡}			
Meerwaldt et al., ²³ cross-sectional (AFR)	T1 and T2 NP+ subjects: 24 T1 and T2 NP– subjects: 23 C: 21	Mean \pm SD SAF	Control: 0.011 \pm 0.001				NP +: 0.025 \pm 0.007 ^{*†} NP –: 0.017 \pm 0.004 [†]		—
Monami et al., ²⁴ cross-sectional (AGE Reader)	T1:— T2: 92 C:—	HR (95% CI)	Each unit of increment of SAF		Arteriopathy of the limbs HR 1.9 (1.1–3.6) <i>Ischemic heart disease</i> HR 1.6 (0.9–2.7) <i>Stroke/TIA</i> HR 1.4 (0.7–2.7)		Neuropathy HR 2.1 (1.1–3.8] Current foot ulcers HR 3.4 (1.6–7.3)	<i>Microalbuminuria</i> HR 1.4 (0.8–2.5) Chronic renal insufficiency HR 2.4 (1.1–5.4)	<i>Retinopathy</i> HR 2.1 (0.9–4.6)
Gerrits et al., ²⁵ prospective (AFR)	T1:— T2: 881 C:—	OR (95% CI)	Each unit of increment of SAF			OR 2.02 (1.45–2.81)	OR 1.50 (1.05–2.14)	OR 1.88 (1.36–2.61)	T2 OR 1.21 [0.83–1.74]
Lutgers et al., ²⁶ prospective (AFR)	T1:— T2: 967 C:—	HR (95% CI)	Below or above median SAF	All-cause mortality HR 2.05 (1.22–3.45)	<i>Cardiovascular events</i> HR 1.46 (0.97–2.20)				
Meerwaldt et al., ²⁷ prospective (AFR)	T1: 48 T2: 69 C: 43	OR (95% CI)	Each unit of increment of SAF	Prospective: cardiovascular mortality: T1 OR 2.00 (1.3–2.7) T2 OR: 2.9 (1.3–4.4)	Cross-sectional: T1 OR 7.8 T2 OR 7.9 (no CIs were given)				

All significant results (significance level: $P < 0.05$) are given in bold type; all results that are not significant are in italic.

Statistics: compared with diabetes patients ^awithout complications and ^bwithout neuropathy, ^cwithout nephropathy, or ^dwithout retinopathy; [†]control subjects without diabetes; or [‡]diabetes patients with microvascular complications. All values mentioned are adjusted for confounding factors.

AFR, autofluorescence reader; C, control subjects without diabetes; CI, confidence interval; HR, hazard ratio; NP+, diabetes patients with neuropathic foot ulceration, NP–, diabetes patients without clinical neuropathy; OR, odds ratios; T1, diabetes mellitus type 1; T2, diabetes mellitus type 2; TIA, transient ischemic attack.

gers et al.²⁶ are adjusted for age, diabetes' duration, sex, smoking, HbA1c, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol.

Results

Characteristics of studies

In total, 141 papers were found. After title and abstract were screened, 134 papers were about different topics and were excluded. Seven papers were included: four^{21–24} were cross-sectional studies, and three^{25–27} were prospective studies. Five of the seven studies were from one research group from Groningen, The Netherlands. Two of the investigators from this group were founders of the company providing the AGE Reader. Characteristics of studies and study participants are described in Table 2. It must be noted that studied populations were very heterogeneous. Studies included subjects with different types of diabetes, treatment, and diabetes' duration, and the participants included were of different ages, with a different history of complications. Studies investigated different outcome (different diabetes complications). The follow-up study of Lutgers et al.²⁶ used the same cohort as the cross-sectional study of Lutgers et al.,²² except for six patients who were lost to follow-up. Gerrits et al.²⁵ also used data from this cohort of patients (a study in a large primary care population of patients with type 2 diabetes). Five studies used the AFR to measure SAF (prototype of the current AGE Reader),^{22,23,25–27} and two studies used the AGE Reader.^{21,24} Different studies adjusted results for different factors (see Supplementary Table S1); it is notable that Gerrits et al.²⁵ did not adjust for age on multivariate analysis. Three of the seven studies compared SAF in diabetes patients with SAF in control subjects without diabetes.^{22,23,27} In these three studies SAF was higher in the diabetes group.

Outcome

A summary of outcomes of all studies is mentioned in Table 3.

All-cause mortality

The only study investigating this end point²⁶ showed a positive association of SAF with all-cause mortality in type 2 diabetes mellitus patients on multivariate analysis (hazard ratio of 2.05 [95% confidence interval (CI) 1.22–3.45] with a median follow-up of 3.1 years).

Cardiovascular mortality

The only study investigating this end point²⁷ found a positive association of SAF with cardiac mortality on multivariate analysis with 5 years of follow-up (OR of 2.00 [95% CI 1.3–2.7] in type 1 diabetes mellitus and 2.9 [95% CI 1.3–4.4] in type 2 diabetes mellitus). The area under a receiver operating characteristic curve using SAF to detect mortality was significantly higher than similar curves using HbA1c (SAF 0.92 vs. HbA1c 0.82 [type 1 diabetes mellitus] and 0.61 [type 2 diabetes mellitus]).

Macrovascular complications

Four studies investigated this end point. Three of these studies found some association of SAF with macrovascular

complications. One study²² showed a significantly higher SAF in diabetes patients with macrovascular complications compared with diabetes patients without complications. They also found a significantly higher SAF in diabetes patients with concomitant micro- and macrovascular complications compared with diabetes patients with only microvascular complications or patients without complications. Meerwaldt et al.²⁷ showed a positive association of coronary heart disease with SAF at their cross-sectional part of the study as well (OR of 7.8 in type 1 diabetes mellitus and 7.9 in type 2 diabetes mellitus [no CIs were given]). Monami et al.²⁴ demonstrated a positive association of SAF with arteriopathy of the limbs, whereas SAF was not associated with ischemic heart disease and transient ischemic attack/stroke. The only prospective study investigating this end point²⁶ did not find a significant association of SAF with cardiovascular events (fatal and non-fatal).

Microvascular complications

The two studies investigating this end point were of different design (cross-sectional/prospective) and showed different results. Lutgers et al.²² found no significant difference in SAF between patients with microvascular complications and patients without complications. In the prospective study of Gerrits et al.,²⁵ however, SAF was a strong predictor of the development of microvascular complications on multivariate analysis (OR of 2.02 [95% CI 1.51–2.80]). Of note is that both studies used data from the same cohort of patients: one described association of SAF and complications cross-sectionally, and the other investigated partly the same patients after a follow-up of 3.1 years.

Different microvascular complications

Neuropathy. The four studies investigating this end point all show a positive association of SAF with neuropathy. One study had a prospective design²⁵ (OR of 1.50 [95% CI 1.05–2.14]), and three studies had a cross-sectional design.^{21,23,24} Meerwaldt et al.²³ demonstrated a significantly higher SAF in diabetes patients with a history of neuropathic foot ulceration compared with diabetes patients without clinical neuropathy. In this study SAF also correlated negatively with both sensory and motor nerve conduction velocities and amplitude. Besides the association with neuropathy, Monami et al.²⁴ found a positive association of SAF with current foot ulceration as well.

Nephropathy. Three studies investigated this end point, and all showed some positive result. One²⁵ showed an OR of 1.88 (95% CI 1.36–2.61) for developing nephropathy with each increment of SAF. Chabroux et al.²¹ also showed an association between SAF and incipient nephropathy (defined as microalbuminuria) as well as overt nephropathy (macroalbuminuria). The third study²⁴ did not show a significant association for microalbuminuria, but it did for chronic renal failure.

Retinopathy

Neither the cross-sectional^{21,24} nor the prospective²⁵ study could demonstrate a significant association of retinopathy with SAF.

Discussion

In this first systematic review on SAF as a noninvasive measure of accumulation of AGEs and diabetes complications, we found that all eligible studies showed a positive association between SAF and one or more diabetes complications (all-cause mortality, cardiovascular mortality, micro- and macrovascular complications, neuropathy, and nephropathy), with the exception of retinopathy. However, these results should be interpreted with caution because the number of studies is limited and there is large heterogeneity between the studies.

The risk of developing micro- and macrovascular complications is not fully explained by the currently established risk factors. Apparently, unknown factors play a role in the pathogenesis of complications; AGEs may be one of them.²⁸ The three prospective studies included in this review showed a significant association of the level of SAF at baseline and development of microvascular complications and the all-cause and cardiovascular mortality rate, even after adjusting for possible confounding factors. Moreover, using a different approach, one of these studies²⁶ also showed that SAF provided additional information to the United Kingdom Prospective Diabetes Study risk score for the estimation of cardiovascular prognosis in type 2 diabetes mellitus. Therefore, SAF might be a promising tool to improve the prediction of complications in the long term.

The association of SAF with diabetes complications does not necessarily mean that this is a causal relationship or that interventions aiming at decreasing SAF will lead to a reduction in chronic organ complications. AGEs have several deleterious effects, such as affecting proteins by changing their three-dimensional structure and activating second messengers and transcription factors by stimulating the receptor for AGEs.^{6,7,28} Therefore it is possible that AGEs not only predict complications but also are a cause of complications. To investigate this, intervention trials with agents that decrease AGE accumulation are required. Multiple studies in animal models have already shown that pharmacological intervention in AGE accumulation has the potential to alleviate end-organ damage.²⁹ However, evidence from clinical studies (in humans) supporting this phenomenon is lacking.²⁹

None of the studies showed any association between SAF and retinopathy. In contrast, the Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) study¹⁶ did demonstrate that AGEs, measured in skin biopsy specimens, can predict the progression of diabetic retinopathy in type 1 diabetes mellitus patients. The discrepancy between these results could be explained by the differences in participants (type of diabetes), differences in duration of the studies (3.1 years in Gerrits et al.²⁵ versus a follow-up of 10 years in the DCCT-EDIC study¹⁶), the difference in the percentage of patients developing (progression of) retinopathy (7% vs. >30%), or differences in defining the outcome (Gerrits et al.²⁵ investigated the development of retinopathy [defined by the presence of at least background retinopathy], whereas the DCCT-EDIC study¹⁶ investigated progression of retinopathy [defined by a worsening of three or more steps on a diabetic retinopathy scale]). Finally, possible differences in pathogenesis between retinopathy and other complications could play a role.

Several study limitations of this review must be noted. First, only seven studies have been published on SAF and complications, and five of these studies are from the same research group (Groningen, The Netherlands). Also, most studies included only small numbers of subjects. Second, only three studies had a prospective design, assessing the predictive value of SAF, instead of a cross-sectional design, in which only an association can be investigated. Third, studies investigated different and mostly multiple outcomes. Most single outcomes were only investigated in one to four separate studies. Also, differences in SAF found in the seven studies were not adjusted for the same factors. In fact, one study even did not adjust for age, a factor known to be strongly associated with SAF. The definitions of the outcomes were different, using a variety of diagnostic tools. For example, Meerwaldt et al.²³ defined the presence or absence of neuropathy by the Dutch Diabetic Neuropathy Symptoms scale and the Dutch Diabetic Neuropathy Examination scale, whereas Chabroux et al.²¹ defined neuropathy by only using a monofilament and a graduated tuning fork.

Conclusions

This systematic review of literature showed an association of SAF with end-organ complications in diabetes, except retinopathy, in all seven studies. However, studies were of large clinical heterogeneity, only three studies had a prospective design, and five studies were from the same research group. More prospective studies, with longer period of follow-up, larger group size, and strict definitions of complications and end points, are needed to demonstrate the potential role and benefit in clinical management before the widespread use of the AGE Reader can be recommended.

Author Disclosure Statement

The authors declare that they do not have any competing interests.

References

1. Fox CS, Pencina MJ, Meigs JB, Vasan RS, Levitzky YS, D'Agostino RB Sr: Trends in the incidence of type 2 diabetes mellitus from the 1970s to the 1990s: the Framingham Heart Study. *Circulation* 2006;113:2914–2918.
2. Winer N, Sowers JR: Epidemiology of diabetes. *J Clin Pharmacol* 2004;44:397–405.
3. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ: Epidemiology of type 1 diabetes. *Endocrinol Metab Clin North Am* 2010;39:481–497.
4. Monnier VM: Nonenzymatic glycosylation, the Maillard reaction and the aging process. *J Gerontol* 1990;45:B105–B111.
5. Miyata T, van Ypersele de SC, Kurokawa K, Baynes JW: Alterations in nonenzymatic biochemistry in uremia: origin and significance of “carbonyl stress” in long-term uremic complications. *Kidney Int* 1999;55:389–399.
6. Singh R, Barden A, Mori T, Beilin L: Advanced glycation end-products: a review. *Diabetologia* 2001;44:129–146.
7. Schmidt AM, Hasu M, Popov D, Zhang JH, Chen J, Yan SD, Brett J, Cao R, Kuwabara K, Costache G, Simionescu N, Simionescu M, Stern D: Receptor for advanced glycation end products (AGEs) has a central role in vessel wall interactions

- and gene activation in response to circulating AGE proteins. *Proc Natl Acad Sci U S A* 1994;91:8807–8811.
8. Koetsier M, Lutgers HL, de Jonge C, Links TP, Smit AJ, Graaff R: Reference values of skin autofluorescence. *Diabetes Technol Ther* 2010;12:399–403.
 9. Cerami C, Founds H, Nicholl I, Mitsuhashi T, Giordano D, Vanpatten S, Lee A, Al-Abed Y, Vlassara H, Bucala R, Cerami A: Tobacco smoke is a source of toxic reactive glycation products. *Proc Natl Acad Sci U S A* 1997;94:13915–13920.
 10. Greven WL, Smit JM, Rommes JH, Spronk PE: Accumulation of advanced glycation end (AGEs) products in intensive care patients: an observational, prospective study. *BMC Clin Pathol* 2010;10:4.
 11. Noordzij MJ, Lefrandt JD, Smit AJ: Advanced glycation end products in renal failure: an overview. *J Ren Care* 2008;34:207–212.
 12. Gerrits EG, Smit AJ, Bilo HJ: AGEs, autofluorescence and renal function. *Nephrol Dial Transplant* 2009;24:710–713.
 13. Beisswenger PJ, Makita Z, Curphey TJ, Moore LL, Jean S, Brinck-Johnsen T, Bucala R, Vlassara H: Formation of immunochemical advanced glycosylation end products precedes and correlates with early manifestations of renal and retinal disease in diabetes. *Diabetes* 1995;44:824–829.
 14. Makita Z, Radoff S, Rayfield EJ, Yang Z, Skolnik E, Delaney V, Friedman EA, Cerami A, Vlassara H: Advanced glycosylation end products in patients with diabetic nephropathy. *N Engl J Med* 1991;325:836–842.
 15. McCance DR, Dyer DG, Dunn JA, Bailie KE, Thorpe SR, Baynes JW, Lyons TJ: Maillard reaction products and their relation to complications in insulin-dependent diabetes mellitus. *J Clin Invest* 1993;91:2470–2478.
 16. Genuth S, Sun W, Cleary P, Sell DR, Dahms W, Malone J, Sivitz W, Monnier VM; DCCT Skin Collagen Ancillary Study Group: Glycation and carboxymethyllysine levels in skin collagen predict the risk of future 10-year progression of diabetic retinopathy and nephropathy in the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications participants with type 1 diabetes. *Diabetes* 2005;54:3103–3111.
 17. Kilhovd BK, Juutilainen A, Lehto S, Ronnema T, Torjesen PA, Hanssen KF, Laakso M: Increased serum levels of advanced glycation endproducts predict total, cardiovascular and coronary mortality in women with type 2 diabetes: a population-based 18 year follow-up study. *Diabetologia* 2007;50:1409–1417.
 18. Meerwaldt R, Links T, Graaff R, Thorpe SR, Baynes JW, Hartog J, Gans R, Smit A: Simple noninvasive measurement of skin autofluorescence. *Ann N Y Acad Sci* 2005;1043:290–298.
 19. Meerwaldt R, Hartog JW, Graaff R, Huisman RJ, Links TP, den Hollander NC, Thorpe SR, Baynes JW, Navis G, Gans RO, Smit AJ: Skin autofluorescence, a measure of cumulative metabolic stress and advanced glycation end products, predicts mortality in hemodialysis patients. *J Am Soc Nephrol* 2005;16:3687–3693.
 20. 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;47:1324–1330.
 21. Chabroux S, Canoui-Poitaine F, Reffet S, Mills-Joncour G, Morelon E, Colin C, Thivolet C: Advanced glycation end products assessed by skin autofluorescence in type 1 diabetes are associated with nephropathy, but not retinopathy. *Diabetes Metab* 2010;36:152–157.
 22. 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;29:2654–2659.
 23. 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;48:1637–1644.
 24. Monami M, Lamanna C, Gori F, Bartalucci F, Marchionni N, Mannucci E: Skin autofluorescence in type 2 diabetes: beyond blood glucose. *Diabetes Res Clin Pract* 2008;79:56–60.
 25. 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;31:517–521.
 26. 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;52:789–797.
 27. Meerwaldt R, Lutgers HL, Links TP, Graaff R, Baynes JW, Gans RO, Smit AJ: Skin autofluorescence is a strong predictor of cardiac mortality in diabetes. *Diabetes Care* 2007;30:107–112.
 28. Goh SY, Cooper ME: Clinical review: the role of advanced glycation end products in progression and complications of diabetes. *J Clin Endocrinol Metab* 2008;93:1143–1152.
 29. Turgut F, Bolton WK: Potential new therapeutic agents for diabetic kidney disease. *Am J Kidney Dis* 2010;55:928–940.

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