

Skin autofluorescence as a measure of advanced glycation endproduct deposition: a novel risk marker in chronic kidney disease

Smit and Gerrits. Current Opinion in Nephrology and Hypertension (2010).

This review article by Smit and Gerrits starts with a summary of the background information on AGEs and a detailed description of the AGE Reader technology. Furthermore it gives a great summary of the AGE Reader validation in several clinical areas.

The main focus of this review is on applications of the AGE Reader in renal disease and the potential of AGE lowering therapies in renal disease. The authors show again that AGEs play a key role in the development and progression of diabetic nephropathy and nondiabetic chronic kidney disease.

The applications of the AGE Reader in diabetic nephropathy are reviewed by the authors. Their conclusion is that the presence and degree of microvascular and macrovascular complications are strongly associated with AGE Reader measurement in both type 1 and type 2 diabetes. This means that the AGE Reader can be used in monitoring the development of diabetic complications.

Besides diabetic complications there are multiple studies performed to assess the potential of the AGE Reader in renal disease. In this review the most important conclusions of these studies are summarized:

- High AGE Reader measurements reported in hemodialysis patients in several studies^{i,ii}.
- The AGE Reader measurement is a strong predictor of mortality in hemodialysis patientsⁱⁱⁱ.
- In patients with CKD, the AGE Reader allows identification of patients with the most marked cardiovascular dysfunction.
- The AGE Reader measurement is a strong predictor of chronic transplant dysfunction and mortality^{iv}. This strongly suggests that AGEs play an important role in the development of chronic transplant dysfunction and mortality.

In the last paragraph the authors review several interventions to reduce AGE levels and the AGE Reader measurement. Several short term studies already showed promising results. The next step in the development of these interventions in kidney disease should be long term studies aimed at preventing microalbuminuria and loss of renal function.

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Skin autofluorescence as a measure of advanced glycation endproduct deposition: a novel risk marker in chronic kidney disease

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Purpose of review

Skin autofluorescence (SAF) is a new method to noninvasively assess accumulation of advanced glycation endproducts (AGEs) in a tissue with low turnover. Recent progress in the clinical application of SAF as a risk marker for diabetic nephropathy as well as cardiovascular disease in nondiabetic end-stage kidney disease, less advanced chronic kidney disease, and renal transplant recipients is reviewed.

Recent findings

Experimental studies highlight the fundamental role of the interaction of AGEs with the receptor for AGEs (RAGEs), also called the AGE–RAGE axis, in the pathogenesis of vascular and chronic kidney disease. SAF predicts (cardiovascular) mortality in renal failure and also chronic renal transplant dysfunction. Long-term follow-up results from the Diabetes Control and Complications Trial and UK Prospective Diabetes Study suggest that AGE accumulation is a key carrier of metabolic memory and oxidative stress. Short-term intervention studies in diabetic nephropathy with thiamine, benfotiamine and angiotensin-receptor blockers aimed at reducing AGE formation have reported mixed results.

Summary

SAF is a noninvasive marker of AGE accumulation in a tissue with low turnover, and thereby of metabolic memory and oxidative stress. SAF independently predicts cardiovascular and renal risk in diabetes, as well as in chronic kidney disease. Further long-term studies are required to assess the potential benefits of interventions to reduce AGE accumulation.

Keywords

advanced glycation endproducts, diabetes, skin autofluorescence

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Introduction

The measurement of skin autofluorescence (SAF) has become a noninvasive method of assessing the accumulation of advanced glycation endproducts (AGEs) as a marker of the long-term impact of glycemic and oxidative stress in humans. Interest in AGEs as a central marker of the so-called metabolic legacy effect has expanded in the context of assessing the long-term effects of early intensive glycemic control in diabetes as well as the metabolic effects of chronic kidney disease (CKD) and chronic renal transplant dysfunction [1,2*]. Kern *et al.* [3*] have recently reported data supporting earlier observations identifying the predictive value of AGEs and AGE fluorescence in diabetic kidney disease in the DCCT–EDIC study [4]. The AGE–RAGE axis is important in many forms of renal disease and suggests new approaches for intervention [5**,6*].

Advanced glycation endproducts: formation and effector pathways

AGEs are formed slowly by the Maillard reaction, which is dependent on glucose levels, but rapid formation of AGEs occurs via another pathway involving reactive carbonyl compounds (RCCs) such as (methyl)glyoxal (the so-called dicarbonyl stress) during oxidative stress. The glyoxalase system forms a defence mechanism against this pathway [7]. A third source of AGEs in humans is the intake of exogenous AGEs from food and smoking [8]. Overall, accumulation of AGEs on proteins with low turnover may result from all three sources: slow glycation, rapid formation via RCCs, and exogenously derived AGEs. When proteins are degraded to the so-called glycation-free adducts and glycation adduct residues, the former in particular are subsequently excreted via the kidney. In the presence of renal failure,

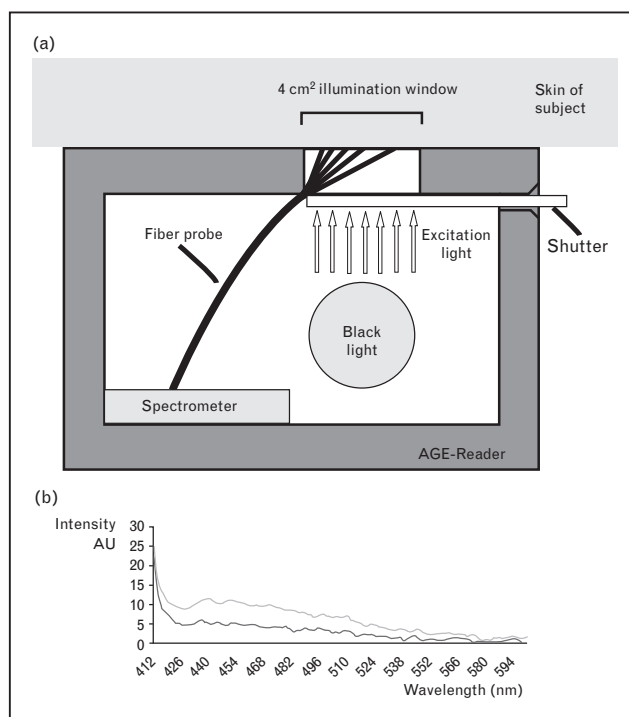
this excretion mechanism fails or is overloaded, and further accumulation on proteins with low turnover may occur. Dicarbonyl stress is also increased in renal failure [9^{*}].

AGEs are no innocent bystanders but exert effects via two pathways. First, they crosslink proteins, nucleic acids and lipids, resulting in structural changes, malfunction, and reduced breakdown. Mitochondrial glycation may in turn enhance oxidative stress, thereby introducing a vicious circle. Second, AGEs bind to cell membrane receptors, the best known of which is the receptor for AGEs (RAGEs). This may lead to activation of intracellular pathways [including prolonged activation of nuclear factor-kappa B (NF- κ B)], and release of cytokines [5^{**},10^{*}], which may induce endothelial dysfunction and other deleterious vascular effects [11].

Development and validation of skin autofluorescence as marker of tissue advanced glycation endproduct accumulation

Several groups have developed devices to easily and rapidly measure SAF for the assessment of AGE accumulation in a point of care setting. In 1997, Jager first noticed increased fluorescence of the skin in diabetic patients during noninvasive capillary microscopy, especially in those with complications. This led to development of the so-called autofluorescence reader, a prototype of the AGE Reader (Diagnoptics Technologies, Groningen, The Netherlands), which became commercially available in 2006. Initial results in patients with diabetes were reported in 1999 and were followed in 2004 by several publications mainly in the field of diabetes and renal failure [12–15]. The principle of the method used in the AGE Reader is shown in Fig. 1 [16,17]. Clinical use of a second device that also utilises SAF to assess AGEs, the so-called SCOUT device (VeraLight, Albuquerque, NM, USA) was first reported in 2007 [18]. The intention of the SCOUT device is to diagnose diabetes. Maynard compared SAF with HbA1c and fasting plasma glucose for the detection of diabetes (confirmed by glucose tolerance test) in a naive population-derived cohort and found superior performance with SAF. No applications in renal failure have been reported to date. Recently, Xu *et al.* [19] reported the development of a SAF device but no clinical data have yet been provided. These three devices, all measuring SAF, are proposed to assess accumulation of AGEs in skin tissue. In the case of the AGE Reader, validation of the level of SAF against specific AGE molecules [pentosidine, carboxymethyllysine (CML) and carboxyethyllysine] was reported in patients with diabetes, renal failure and healthy controls [12,13]. In a combined analysis, 76% of the variance in SAF level could be explained by the variance in dermal pentosidine levels in skin biopsies. The molecular nature of collagen-

Figure 1 Diagrammatic presentation of the advanced glycation endproduct reader and examples of the light intensity differences



(a) An ultraviolet A light source with a peak wavelength of 370 nm illuminates a small skin area; the reflected and fluorescent light coming back from the skin is detected by a fiber and fed into a spectrometer for further analysis. (b) Examples of the light intensity differences in skin fluorescence spectra in the 420–600 nm range between a patient with diabetes (upper tracing) and a healthy control (lower tracing). The left side of the panel shows the peaked-off light intensities of the light source with a peak wavelength around 370 nm. Skin autofluorescence is the ratio between the light intensities in the 420–600 nm range divided by the light intensity in the 300–420 nm range. (a) Reproduced with permission from [16]. (b) Reproduced with permission from [17].

linked fluorescence in diabetes and end-stage kidney disease (ESKD) has been partially characterized by the detection of a major fluorophore, LW-1, with a molecular weight of 623 Da [20].

AGEs are stable endproducts and form irreversible links in tissues with low turnover. The extent to which proteins are modified by accumulation of AGEs is an essential determinant of their functional and structural effects. Consequences of AGE modification are more important in tissues with low turnover, such as the dermis and glomerular and tubular basement membranes, than in blood or urine. Januszewski *et al.* [21] showed a strong correlation between SAF and AGE-related fluorescence of the eye lens, another tissue in which proteins with low turnover are present. Examples of how SAF may reflect functional and structural tissue damage better than plasma AGE levels are discussed below.

Advanced glycation endproducts and receptor for advanced glycation endproducts in renal disease

Diabetic nephropathy is the classic model for demonstrating the pathogenic role of AGEs and RAGEs. Glomerulosclerosis in diabetic animals is associated with AGE deposition in mesangium as well as hyalinized and/or sclerotic lesions. Mesangial cell function is also altered after modification of collagen IV by glucose or methylglyoxal [22[•]]. Overexpression of RAGEs accelerates the development of glomerulosclerosis in mice [23]. In RAGE knockout models and during inhibition of AGE formation, the development of diabetic nephropathy, with respect to both micro-albuminuria and renal function loss, is prevented (see further below) [24[•]].

AGEs also accumulate in nondiabetic uremic patients despite their normal serum glucose levels. Among hemodialysis patients, both diabetic patients and nondiabetic individuals have high plasma pentosidine and CML levels. Patients with less advanced stages of CKD show a relation between AGE levels (CML) and renal function in selected groups and in the general population [25]. Hou *et al.* [26] proposed that AGEs and RAGEs may contribute to amplification of inflammation in nondiabetic CKD. Plasma pentosidine levels and RAGE expression on monocytes strongly increased in parallel with tumor necrosis factor, neopterin and CRP levels in patients with worsening (nondiabetic) CKD.

In diabetic and nondiabetic patients with ESKD, peritoneal dialysis treatment causes low-grade chemical peritonitis due to the limited biocompatibility of peritoneal dialysis fluids that contain high glucose concentrations and, therefore, glucose-derived products that are precursors of AGEs. Because RAGE is expressed on endothelial and mesothelial cells, the receptor may bind AGEs generated endogenously or formed during peritoneal dialysis. The binding of AGEs to RAGEs produces a local inflammatory reaction, likely as a consequence of vascular cell adhesion molecule-1 overexpression, leukocyte adhesion, and cytokine release.

The role of RAGEs in the pathogenesis of CKD has been reviewed in detail recently [5^{••}] and in the broader context of vascular disease by Yan *et al.* [10[•]] from the same group. A more critical view on the relevance of RAGEs in the development of ESKD has been provided by Thornalley and Rabbani [9[•]], who question the relevance of the experimental studies with often highly glycosylated AGE-modified proteins for development of human renal failure when plasma protein glycation is less marked. However, it must be noted that the degree of AGE modification of proteins in tissues with low turnover may be considerably higher than in plasma.

Thornalley and Rabbani draw attention to another potentially relevant function of the RAGE receptor, namely decreased expression of glyoxalase 1, a component of antiglycation defence mechanisms in response to S100A12 protein, making the vasculature vulnerable to dicarbonyl stress and related AGE formation.

Skin autofluorescence in diabetic nephropathy, and prediction of macrovascular complications

Initial clinical studies were performed in diabetes mellitus, because it is the classic example of increased formation and accumulation of AGEs. SAF was indeed found to be approximately 30% higher in patients with type 1 or type 2 diabetes mellitus compared with age-matched controls. In a large cohort of well controlled primary care patients with type 2 diabetes, the presence and degree of microvascular and macrovascular complications were associated with a graded increase in SAF [15]. Gerrits *et al.* [27] reported that SAF is not only associated with diabetic nephropathy, but is also a predictor of its development.

SAF was also an independent and strong predictor of macrovascular complications as well as mortality. Compared with the different variables in the UK Prospective Diabetes Study (UKPDS) risk engine, SAF was the best single predictor, after calendar age, of total and cardiovascular mortality. SAF also adds predictive value to the UKPDS risk engine, resulting in risk reclassification in 25–30% of patients [28^{••}].

The association of SAF with diabetic nephropathy was recently extended to type 1 diabetes [29]. Additionally, Conway *et al.* [30] showed that in type 1 diabetes SAF, as measured with the SCOUT device, correlates strongly with coronary artery calcification (CAC) such that SAF evidenced a high level of discrimination for detecting CAC scores greater than 400 (area under the curve of receiver operating characteristic curve 85%).

Skin autofluorescence in renal disease

High levels of SAF, even substantially higher than in patients with diabetes and complications, have been reported in several hemodialysis cohorts [13,31,32]. Diabetic hemodialysis patients had slightly higher levels than nondiabetic hemodialysis patients. McIntyre and Chesterton [33] extended these observations to peritoneal dialysis patients and reported similarly increased SAF values. In peritoneal dialysis patients, SAF correlated with dialysis vintage and also strongly with historical peritoneal dialysis glucose exposure, whereas there was no difference between diabetic and nondiabetic peritoneal dialysis patients. During a follow-up period

of 3 years, SAF appeared to be a strong predictor of mortality in hemodialysis patients, independent of previous cardiovascular disease [13]. In a report from the Renal Risk in Derby (RRID) primary care cohort, McIntyre reported that SAF is related to estimated glomerular filtration rate (eGFR) in CKD stage 3 independent of age, the presence of diabetes and smoking (N. McIntyre, Determinants of skin autofluorescence in CKD stage 3 patients, Poster F-PO1124 American Society of Nephrology, 2009). SAF was also independently associated with a history of cardiovascular disease. In another cohort of patients with type 2 diabetes and moderate nephropathy, Gerrits *et al.* [32] found that SAF correlated with eGFR categories. Similarly, Chabroux *et al.* [29] confirmed the association of SAF with diabetic nephropathy in patients with type 1 diabetes.

In hemodialysis patients, SAF is also related to several markers of cardiovascular dysfunction. SAF was independently associated with diastolic left ventricular function, whereas plasma AGEs were not [34]. Ueno *et al.* [31] found that SAF is strongly and independently associated with pulse wave velocity (PWV) as a marker of arterial stiffness in ESKD (but also in controls). Ueno *et al.* also recently reported that in ESKD patients both SAF and serum pentosidine correlated with carotid intima media thickness (IMT), and that SAF was inversely related endothelial progenitor cell (EPC) levels, whereas such a correlation was not observed with serum pentosidine. In multiple regression analysis SAF, but not serum pentosidine or IMT, was related to EPC levels [35[•]]. In the RRID cohort, McIntyre found a positive and independent correlation between SAF and PWV in patients with CKD stage 3 (N. McIntyre, Determinants of skin autofluorescence in CKD stage 3 patients, Poster F-PO1124 American Society of Nephrology, 2009). Thus, in patients with CKD, SAF allows the identification of patients with the most marked cardiovascular dysfunction.

In hemodialysis patients, a population with a high annual mortality, SAF is an independent indicator of those at highest risk. However, the clinical value of this information may seem limited in the absence of effective treatments. Conventional methods of renal replacement therapy are only partially effective with regard to AGE clearance, and the degree of removal is dependent on the frequency as well as the duration of dialysis [36]. Also, the dialysis procedure itself may contribute to AGE accumulation: oxidative stress is an important factor leading to AGE formation, and hemodialysis membranes, depending on their degree of biocompatibility, probably contribute to increased AGE formation. In contrast, new technologies including high-flux membranes, vitamin E-coated low-flux dialyzers and convective therapies may provoke less oxidative stress and result in enhanced AGE removal in hemodialysis patients [37]. Preliminary

evidence suggests that high-flux hemodialysis and the use of low-glucose dialysate in peritoneal dialysis are associated with lower levels of circulating AGEs and SAF (S. Arsov, personal communication; manuscript in preparation).

Peritoneal dialysis solutions with a lower glucose content may also reduce serum AGEs as a result of reduced glycaemic stress. The use of peritoneal dialysis fluids low in glucose degradation products results in prolonged technique survival and (more importantly) also significant patient survival [38]. Preliminary data show that SAF is also lower in peritoneal dialysis patients on low or no glucose-containing dialysate (N. McIntyre, *et al.*, unpublished data). These findings suggest that lower tissue AGE accumulation over time could be due to lower serum AGE levels and may limit resulting tissue damage.

The results of ongoing studies investigating the independent predictive value of SAF for cardiovascular risk and further renal function loss in earlier stages of CKD are awaited to assess its clinical value.

Our study group has also investigated the reversibility of AGE accumulation in renal transplantation. Kidney transplantation represents one of the most effective approaches to reduce the markedly increased AGE accumulation in dialysis patients, although AGE and SAF levels remain well above those of controls. Follow-up studies in kidney transplant patients reveal a slow fall of skin fluorescence levels several months after transplantation (A.J. Smit, personal communication). Moreover, the degree of persisting AGE accumulation after renal transplantation might be involved in the accelerated development of cardiovascular disease and chronic renal transplant dysfunction [39]. Increased levels of SAF are indeed associated with several risk factors for chronic renal transplant dysfunction and cardiovascular disease [40]. Importantly, in a large group of patients with a previous kidney transplant SAF was found to be a strong predictor of chronic transplant dysfunction and mortality in the following 5 years [2[•]]. This strongly suggests that AGEs play an important role in the development of chronic transplant dysfunction and mortality, probably by accelerating systemic and renal atherosclerosis. SAF may prove valuable for assessing this risk in the post-transplant period.

Interventions to reduce advanced glycation endproduct and skin autofluorescence levels as well as clinical endpoints in renal disease

Several approaches directed at reducing the effects of AGEs have been evaluated in models of diabetic nephropathy for reduction of microalbuminuria or slowing renal function decline. In experimental studies by Tan *et al.*

[24•] in an obese diabetic mouse model, suppression of RAGE expression within a RAGE^{-/-} genotype, and administration of alagebrium, an inhibitor of AGE accumulation, each prevented renal damage and evidenced additive benefit, whereas feeding a low-AGE diet did not. The classic anti-AGE compound, aminoguanidine, an inhibitor of AGE formation, reduced microalbuminuria in experimental models but has not been successful in clinical trials because of side-effects [41]. Novel AGE breakers such as TRC418 have shown reduction of albuminuria and renal function loss in diabetic rats and are in development in human studies [42]. In a merged dataset from two clinical studies, pyridoxamine was reported to reduce change from baseline in serum creatinine, but not microalbuminuria [43]. Further development was, however, halted due to side-effects. Furthermore, aggravation of renal damage was found in other animal models when pyridoxamine was used in combination with ACE inhibitors. Thornalley and co-workers [44] reported a protective effect of thiamine and benfotiamine in a rat model of diabetic kidney disease. They also reported a modest reduction of microalbuminuria in a small short-term study in type 2 diabetes mellitus (T2DM) patients using high-dose thiamine [45], but Alkhalaf *et al.* [46] failed to find reduction of microalbuminuria or urinary excretion of the tubular damage marker KIM-1 in T2DM patients. Experimental studies using ACE inhibitors or angiotensin-receptor blockers (ARBs) to inhibit the renin-angiotensin-aldosterone system (RAAS) have reported reduced AGE formation [47]. This effect of RAAS inhibition is at least partially modulated by the RAGE receptor. Several experimental studies using ARB treatment have shown reduction in tubular and glomerular AGE accumulation along with reduction of renal function loss, tubular damage parameters and proteinuria [48]. In one small ($n = 11$ diabetic retinopathy patients) 12-week clinical study, candesartan reduced urinary CML excretion, but not albuminuria. No other formal controlled studies of ARB treatment and its effect on AGE formation in diabetic nephropathy have been performed, but in a recent post-hoc analysis of the irbesartan diabetic nephropathy trial study in T2DM nephropathy irbesartan did not alter the increase in pentosidine and CML in serum and gave only minimal reduction in renal function loss after 2 years of treatment [49].

One of the fundamental problems with these intervention studies may be their very short time frame: it seems improbable that a 3-month or even a 2-year treatment period would result in improvement in a condition associated with accumulation of AGEs in tissues with low turnover, such as the basement membrane of the glomeruli or tubules, that may have taken years to provoke microalbuminuria or renal function loss. There is an urgent need for long-term studies (>2 years) that are

aimed at preventing microalbuminuria and renal function loss rather than reversing it. In nondiabetic CKD the role of low-AGE diets should also be explored in long-term studies. Dietary AGEs seem to exert negative effects, especially once urinary excretion of AGE-free adducts becomes reduced with loss of glomerular filtration capacity [50]. Finally, the predictive role of SAF levels for mortality and chronic graft dysfunction, several years after renal transplantation, supports the concept of limited and slow reversibility of AGE-induced damage.

Conclusion

AGEs play a pivotal role in the development and progression of diabetic nephropathy but also of nondiabetic CKD. SAF has been validated as a simple, non-invasive method for assessment of AGE content in a tissue with low turnover. SAF as marker of AGE accumulation is a strong and independent predictor of nephropathy and also cardiovascular complications in diabetes. Similarly, in nondiabetic CKD, SAF is related to vascular dysfunction and predicts mortality in ESKD. After renal transplantation SAF is a valuable predictor of chronic transplant dysfunction and mortality. The investigation of interventions aimed at reducing AGE accumulation in patients with renal damage should move from short-term studies in patients with established renal damage to long-term prevention in an early phase of diabetes or CKD.

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References and recommended reading

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- of special interest
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