Skin Autofluorescence: an emerging biomarker in persons with kidney disease

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Abstract

Purpose of review: Skin autofluorescence (SAF) is a measure of the accumulation of advanced glycation end-products (AGEs) proposed to act as a marker of "cumulative metabolic stress". This paper discusses mechanisms of AGE formation and reviews published literature on SAF as a biomarker and risk factor across the spectrum of kidney disease.

Recent findings: SAF is elevated in adults and children on dialysis. Higher SAF is an independent risk factor for cardiovascular and all-cause mortality in persons receiving haemodialysis and for all-cause mortality in persons performing peritoneal dialysis, though the increase in discrimination when SAF was added to traditional risk factors was modest. In less advanced chronic kidney disease, higher SAF predicts all-cause mortality and progression. SAF is elevated in renal transplant recipients, but to a lesser extent than in dialysis patients. In one study higher SAF predicted graft loss and mortality. SAF has been reported to be increased in patients with acute kidney injury.

Summary: A growing body of evidence attests that SAF, a marker of AGE accumulation, is a risk factor for mortality and kidney function decline in multiple types of kidney disease. Further studies are warranted to evaluate interventions to reduce SAF and the impact on clinical outcomes.

Keywords: advanced glycation end-products, chronic kidney disease, dialysis, kidney transplant, skin autofluorescence

Introduction

Advanced glycation end products (AGEs) are reactive, cross-linking moieties that are proposed to play a role in the pathogenesis of age related diseases as well as cardiovascular disease (CVD) and the complications of diabetes mellitus [1]. The observation that some AGEs fluoresce in ultraviolet light led to the development of a non-invasive method to assess tissue accumulation of AGEs by measurement of skin autofluorescence (SAF). Subsequent clinical studies have confirmed that SAF increases with age and is elevated in persons with diabetes. Moreover, SAF has been identified as an independent predictor of all-cause mortality and cardiovascular events in persons with diabetes or cardiovascular disease [2] and in a large general population study [3]. AGEs are normally excreted in part by the kidneys and can therefore also be regarded as uraemic toxins. In this paper we review the increasing body of evidence that the assessment of AGE accumulation by SAF is a potentially important biomarker to evaluate risk in persons with all categories of kidney disease.

Formation of Advanced Glycation End Products

AGEs form as a result of glycation and oxidation of amino groups on proteins as well as lipids and nucleic acids. This occurs non-enzymatically over time through a series of complex steps termed the Maillard reaction, particularly in the presence of hyperglycaemia. Additionally, AGEs may be formed more rapidly through reactions with α-dicarbonyls formed as a result of oxidative stress [1]. Exogenous sources of AGEs also contribute to AGE accumulation. AGEs exist naturally in uncooked food, particularly animal products with high fat and protein content. Furthermore cooking food at high temperatures or with dry heat (e.g. grilling, frying or baking) induces

substantial AGE formation, increasing the AGE content by 10 to 100 fold compared with uncooked food [4]. Detailed studies have estimated that approximately 10% of ingested dietary AGEs are absorbed [5]. Tobacco smoking is a further exogenous source of AGEs which are thought to be formed in tobacco during the curing process. Reactive glycation products have been identified in tobacco and tobacco smoke that can react rapidly with proteins to form AGEs [6]. Finally AGEs are partially renally excreted and reduced renal function therefore contributes to AGE accumulation [5].

AGEs are proposed to contribute to the pathogenesis of cardiovascular and other diseases through two principal mechanisms. First, they form cross-links between structural proteins including collagen and elastin in arterial walls resulting in arterial stiffness [7]. Second, AGEs bind to a receptor of AGE (RAGE) and provoke endothelial dysfunction [8] as well as inflammatory responses which likely contribute to the pathogenesis of atherosclerosis [9] and chronic kidney disease (CKD) [10]. The accumulation of AGEs on proteins with slow turnover has been proposed to serve as a measure of “cumulative metabolic stress” [11].

Skin Autofluorescence Measurement

The measurement of SAF is non-invasive, operator independent and takes only a few minutes. Devices for measuring SAF have been developed and are commercially available. The equipment shines ultraviolet light on an area of skin, usually on the forearm, and detects emitted fluorescence with a spectrometer (Figure 1). SAF is calculated by dividing the average intensity of emitted light in the range 420 to 600 nm by the average intensity excitation light in the range 300 and 420 nm,

multiplied by 100 and is expressed in arbitrary units (AU) [11]. Results can also be compared with age standardised normal values and expressed as a z-score [3]. SAF measurements have been reported to have a coefficient of variation of 7-8% [12]. Readings vary slightly between arm and leg measurements and the site should therefore be standardised [13]. One important limitation of the current method for measuring SAF is that it cannot be used in persons with very dark skin colour (Fitzpatrick skin colour type V-VI) due to high absorption of the excitation light (i.e. skin reflectivity below 6%). If skin reflectivity is <6% the equipment indicates that the signal is too low to obtain a valid reading. Nevertheless, SAF has been measured in persons of African and Afro-Caribbean origin [14].

SAF in Persons with End-Stage Kidney Disease

Haemodialysis

A landmark paper that provided the first clear evidence that SAF is an independent risk factor for all-cause and cardiovascular mortality in persons with kidney disease was conducted in 109 patients receiving haemodialysis (HD). At baseline, SAF levels were 2.4-fold higher than in controls and independent determinants of SAF included age, duration of renal failure, duration of dialysis, diabetes, serum triglycerides and C reactive protein (CRP). After three years of follow-up 42 participants (39%) had died and SAF was identified as an independent risk factor for all-cause mortality (OR 3.9; 95% CI, 1.9 to 8.1) along with previous CVD, serum albumin and CRP. SAF was also an independent risk factor for cardiovascular mortality (OR 6.8; 95% CI, 2.6 to 17.5) which accounted for 55% of the deaths [11]. In a subgroup of 29 patients, SAF was shown to correlate strongly with collagen-linked fluorescence in skin biopsies and with circulating AGE concentrations [11]. Several subsequent studies as well as

a meta-analysis [2] have confirmed higher SAF as an independent risk factor for all-cause [15, 16] and cardiovascular mortality [17] on HD. Additionally, one study has found that the magnitude of increase in SAF over one year was an independent predictor of subsequent mortality on HD [18]. Furthermore, higher SAF has been reported to be independently associated with CVD [19] and several factors that contribute to CVD in HD patients, including arterial stiffness [20] endothelial dysfunction (determined by flow mediated dilatation) [21] and diastolic dysfunction [22]. Recently, a cross-sectional analysis in 120 persons receiving HD reported that SAF was significantly higher in those with malnutrition (identified by Subjective Global Assessment) versus those who were well nourished [23]. Interestingly, dietary AGE intake was not associated with SAF. In a multivariable analysis, several markers of malnutrition including lower serum albumin, lower dietary protein intake and lower hand grip strength were identified as independent determinants of higher SAF (together with longer dialysis vintage, diabetes and history of smoking). This observation raised the possibility that the association between SAF and increased mortality on HD may in part be explained by the previously reported association between malnutrition and increased mortality [24]. Prospective studies are in progress to evaluate this further.

Peritoneal Dialysis

SAF levels have also been reported to be elevated in persons performing peritoneal dialysis (PD). In one study SAF was found to be similar in PD versus HD patients, though dialysis vintage was significantly lower in the PD population [25]. In contrast, another study reported higher SAF in HD patients [26]. Two studies that compared SAF in PD versus HD patients after adjustment for dialysis vintage and other

potential confounders found higher SAF in participants on PD [27, 28]. A key factor that likely contributes to AGE accumulation in during PD is exposure to the glucose present in PD fluid. Several studies have confirmed this by showing a significant positive association between the magnitude of glucose exposure and SAF [25, 27, 28]. A further consideration is that heat sterilisation of PD fluid results in formation of glucose degradation products (GDP) which in turn promote AGE formation in the body. One study investigated the use of dual chamber PD solutions (in which the glucose is stored in an acidic solution resulting in less GDP formation during heat sterilisation) versus standard single chamber PD solutions. Participants using dual chamber solutions evidenced significantly lower SAF in a univariable analysis (median SAF 3.39 (2.69 to 3.98) AU versus 3.5 (3.05 to 4.54) AU; p=0.04) but this difference was no longer significant after multivariable adjustment [29]. Similar to observations in HD, SAF has been identified as a risk factor for increased mortality in persons performing PD [30, 31], though multivariable analyses were not performed in these studies.

Stage 5 Chronic Kidney Disease

A study in a mixed population of persons with predialysis CKD stage 5 (n=130) or on PD (n=93) and HD (n=38) investigated the association of SAF and a measure of arterial stiffness, augmentation index (AIx), with all-cause and cardiovascular mortality in relation to traditional risk factors evaluated using the Framingham Risk Score (FRS) [32]. Both SAF and AIx predicted these outcomes but the increase in discrimination when they were added to the FRS was relatively modest (for all-cause mortality: area under the receiver operator characteristic curve (AUROC) for FRS of 0.77 increased to 0.79 with addition of SAF and 0.79 with addition of AIx; for

cardiovascular mortality: AUROC for FRS of 0.72 increased to 0.75 with addition of SAF and 0.78 with addition of AIx). In Cox proportional hazards models, SAF remained a significant predictor of all-cause mortality after adjustment for the FRS but not after additional adjustment for the presence of CVD, CRP and serum albumin [32]. Thus SAF was confirmed as a risk factor for mortality but traditional risk factors accounted for most of the observed risk.

SAF in Children with Chronic Kidney Disease

AGE accumulation is regarded as a process that occurs slowly over time and with increasing age, but the extent to which this is accelerated in the setting of CKD, and particularly ESKD, is illustrated by a study that included 76 children (mean age 14.3 to 15.0 years): 20 on HD, 20 on PD and 36 with CKD stage 2-4. Similar to observations in adults, children with CKD evidenced substantially higher SAF than healthy controls (HD: 2.61±0.57 AU, PD: 2.46±0.72 AU, CKD: 1.9±0.46 AU, controls: 1.33±0.26 AU; $p<0.001$) [33]. Moreover, higher SAF correlated with multiple markers of CVD including pulse wave velocity, left ventricular mass index and blood pressure as well as serum markers of endothelial dysfunction and vascular disease, in particular, E-selectin and matrix metalloproteinase-9, which remained associated with SAF in a multivariable analysis [34]. In children receiving dialysis, SAF correlated with dialysis vintage and in those not receiving dialysis SAF was inversely related to creatinine clearance [33].

SAF in Less Advanced Chronic Kidney Disease

SAF has also been investigated in persons with less advanced CKD, not requiring renal replacement therapy. In the largest study to date, SAF was observed to be

elevated versus historical controls in 1707 persons with relatively mild CKD (mean estimated GFR 52.5±10.4 ml/min/1.73m^2). Furthermore, SAF was found to correlate with several markers of increased renal and cardiovascular risk, and was independently and negatively associated with estimated GFR [12]. After a mean follow-up of 3.6 years, SAF was associated with increased all-cause mortality in univariable analysis and after adjustment for age and sex, though the association was no longer statistically significant after adjustment for multiple risk factors [35]. Furthermore SAF has been reported to associate with multiple manifestations of CVD in persons with CKD including arterial stiffness [12], subclinical atherosclerosis [36] and coronary artery calcification [37]. SAF has also been reported to be an independent predictor of CKD progression. In a study of 245 persons with at least two traditional risk factors for CVD and normal or mildly reduced GFR (66.7±18.6 mL/min/1.73m^2), higher SAF predicted rapid GFR decline (defined as >3 ml/min/1.73m^2/year) [38] and among 449 persons with CKD recruited from nephrology departments, higher SAF was an independent risk factor for the combined outcome of doubling of serum creatinine or ESKD over a median of 39 months [39].

SAF in Renal Transplant Recipients

SAF has been investigated in persons with a functioning renal transplant, who represent an interesting group because they have previously experienced ESKD. In a cross-sectional analysis that included 285 renal transplant recipients, mean SAF was found to be elevated (2.7±0.8 AU) and was independently associated with age, systolic blood pressure, CRP, pre-transplant dialysis duration, creatinine clearance at baseline and change in creatinine clearance after 1 year, as well as smoking

history and plasma vitamin C levels [13]. A similar analysis in 189 renal transplant recipients confirmed elevated SAF (3.0±0.8 AU) and reported associations with multiple similar factors as well as markers of subclinical atherosclerosis including ankle brachial index and transplant kidney resistivity index [40]. A further study compared SAF levels in dialysis patients, renal transplant recipients and persons with CKD stage 3 (similar mean GFR to the transplant recipients) and found that SAF was highest in dialysis patients but similar in transplant recipients and those with CKD (mean SAF HD: 3.7±0.9 AU; PD: 3.6±0.8 AU; transplant recipients: 2.8±0.6 AU; stage 3 CKD: 2.8±0.7 AU). This implies that SAF may decrease post renal transplantation but remains elevated at the levels that one would expect due to reduced GFR [41]. In a small number of patients with pre-transplant SAF measurements, a decrease in SAF was observed at a mean of 16 months post transplantation [41]. A prospective study evaluating the value of SAF as a risk factor in 302 renal transplant recipients observed that higher SAF was an independent predictor of the combined outcome of graft loss and all-cause mortality after a mean follow-up of 5.2 years (HR 1.83; 95% CI, 1.22 to 2.75) [42].

SAF in Acute Kidney Injury

One small study has evaluated SAF in the setting of acute kidney injury (AKI). SAF was elevated in 35 persons with AKI (3.0±0.7 AU) but was lower than in a group of 35 persons with ESKD of similar age (3.7±0.7 AU). SAF also correlated with the duration of kidney failure after adjustment for age and sex, and was found to increase from 2.6±0.7 AU to 3.0 ± 0.7 AU ($p<0.05$) when repeated in six of the persons with AKI after a mean of 10 days, supporting the notion that AGEs accumulate rapidly during AKI [43].

Interventions to Reduce SAF

The observation of an association between higher SAF and all-cause as well as cardiovascular mortality in diverse study populations [2] and the proposed mechanisms whereby AGE accumulation may contribute to the pathogenesis of CVD, raises the possibility that reducing AGE accumulation may ameliorate the development of CVD. In small, short term randomised studies in dialysis patients, allocation to a low AGE diet was associated with a reduction in serum AGE concentrations but SAF was not evaluated [44, 45]. One cross-sectional observational study investigated the impact of a vegetarian diet, predicted to be low in AGE content, on SAF in persons on HD. Lower mean SAF was observed in 27 vegetarian HD patients when compared to 305 non-vegetarian HD patients (SAF 2.7±0.6 versus 3.3±0.97 AU; p=0.002) and in a multivariable analysis vegetarian diet remained an independent determinant of lower SAF [14]. No prospective studies have yet investigated the effect of reducing dietary AGE intake on SAF in persons with CKD, though in the light of the evidence presented above, care would have to be taken to avoid causing malnutrition, particularly in dialysis patients. Other interventions that may potentially reduce AGE accumulation and therefore SAF include smoking cessation, antioxidant therapies, high flux HD and reduced glucose exposure from PD fluid but none of these have yet been evaluated prospectively. Moreover, it remains to be established whether a reduction in SAF will be associated with a corresponding reduction in all-cause or cardiovascular mortality.

Conclusions

A growing body of evidence attests that SAF, a marker of AGE accumulation, is a risk factor for all-cause mortality, cardiovascular mortality and kidney function decline in multiple types of kidney disease. However, it has not yet been ascertained whether SAF can be reduced in persons with kidney disease or whether such a reduction will result in a decrease in the associated risks. Further studies are warranted to evaluate interventions to reduce SAF and the impact of these on clinical outcomes.

Key Points

- Skin autofluorescence (SAF) is a non-invasive measure of the accumulation of advanced glycation end-products and is proposed to act as a marker of "cumulative metabolic stress".
- SAF is markedly elevated in persons on dialysis and, to a lesser extent, in those with a renal transplant and less advanced chronic kidney disease (CKD).
- Higher SAF is a risk factor for mortality in persons on dialysis or with CKD and predicts kidney function decline in those with CKD or a kidney transplant.
- Further studies are warranted to evaluate interventions to reduce SAF and the impact of these on clinical outcomes in persons with kidney disease.

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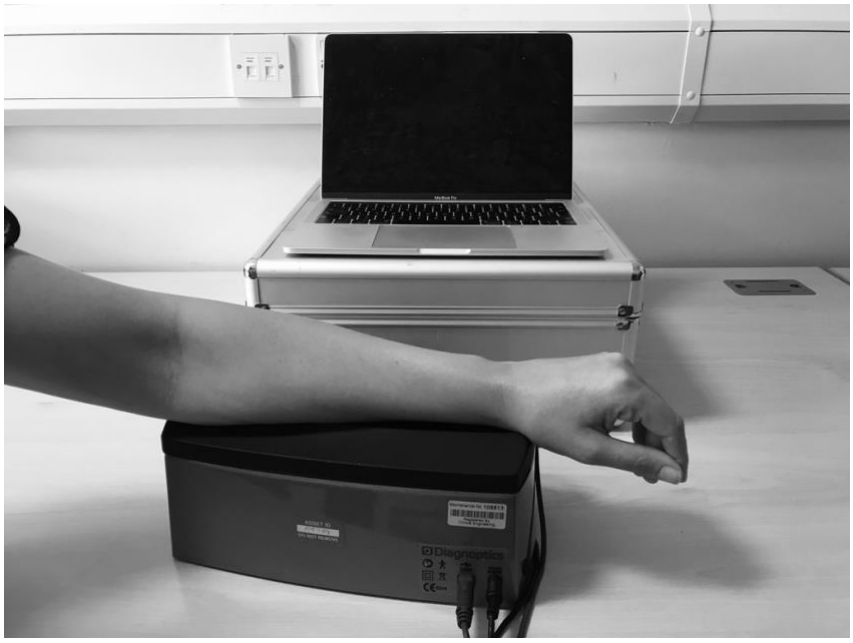
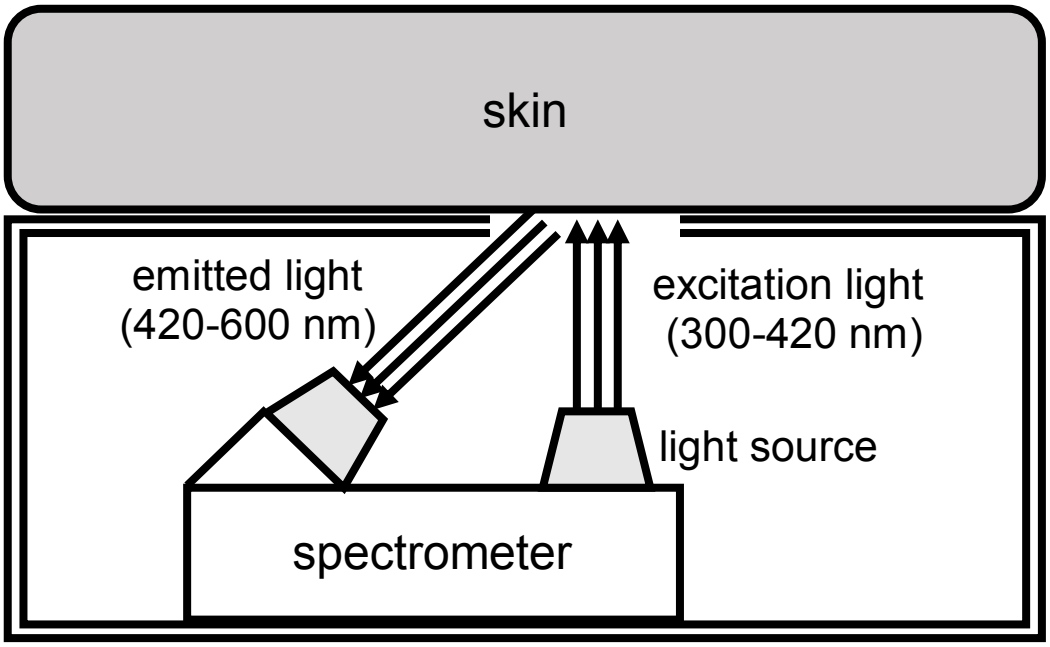
Figure Legends

Figure 1. Photograph of a skin autofluorescence reader (A) and a diagram illustrating the method of operation (B).

A



B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