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*Published in:*
Methods

*DOI:*
10.1016/j.ymeth.2021.02.016

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*
Publisher's PDF, also known as Version of record

*Publication date:*
2022

Link to publication in University of Groningen/UMCG research database

*Citation for published version (APA):*
Atzeni, I. M., van de Zande, S. C., Westra, J., Zwerver, J., Smit, A. J., & Mulder, D. J. (2022). The AGE reader: a non-invasive method to assess long term tissue damage. *Methods*, *203*, 533-541. https://doi.org/10.1016/j.ymeth.2021.02.016

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Methods 203 (2022) 533–541

Contents lists available at ScienceDirect

Methods

journal homepage: www.elsevier.com/locate/ymeth

# The AGE Reader: A non-invasive method to assess long-term tissue damage

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ARTICLE INFO

*Keywords:*
AGE Reader
Advanced glycation endproducts
Skin autofluorescence

ABSTRACT

*Aims:* Advanced glycation endproducts (AGEs) are sugar-modified adducts which arise during non-enzymatic glycoxidative stress. These compounds may become systemically elevated in disease states, and accumulate in tissue, especially on long-lived proteins. AGEs have been implicated in various acute, and chronic diseases, stressing the need for reliable and comprehensive measuring techniques. Measurement of AGEs in tissue such as skin requires invasive skin biopsies. The AGE Reader has been developed to assess skin autofluorescence (SAF) non-invasively using the fluorescent properties of several AGEs.

*Results/conclusion:* Various studies have shown that SAF is a useful marker of disease processes associated with oxidative stress. It is prospectively associated with the development of cardiovascular events in patients with diabetes, renal or cardiovascular disease, and it predicts diabetes, cardiovascular disease, and mortality in the general population. However, when measuring SAF in individual subjects, several factors may limit the reliability of the measurement. These include endogenous factors present in the skin that absorb emission light such as melanin in dark-skinned subjects, but also factors that lead to temporal changes in SAF such as acute diseases and strenuous physical exercise associated with glycoxidative stress. Also, exogenous factors could potentially influence SAF levels inadvertently such as nutrition, and for example the application of skin care products. This review will address the AGE Reader functionality and the endogenous, and exogenous factors which potentially influence the SAF assessment in individual subjects.

## 1. Introduction

Advanced glycation endproducts (AGEs) are sugar-modified adducts which bind to amino acids of proteins, and accumulate on proteins with a slow turnover. AGEs are formed by a process of non-enzymatic glycation and oxidation during aging.

Accumulation of AGEs has been implicated in several diseases. Plasma and tissue AGEs are higher in diseases such as diabetes mellitus [1–3], cardiovascular disease (CVD) [4,5], chronic kidney disease [6], and autoimmune diseases [7,8]. AGE levels may provide information about existing damage in chronic diseases [9,10], and measuring these levels might allow earlier identification of modifications in diseases, giving the possibility of investigating, reversing, and/or slowing down the process of accelerated aging.

The level of AGEs in the body can be measured in serum and/or plasma, however, these AGEs do not correctly reflect levels of AGEs in tissue [11]. This is due to the high turnover rate of the large majority of proteins in the circulation in comparison to most long-lived proteins in tissue, such as collagen. To assess AGE levels in tissue, biopsies are necessary, and taking biopsies is an invasive procedure, and cannot be performed on a large scale basis. The AGE Reader (DiagnOptics Technologies BV, Groningen, The Netherlands) has been developed to non-invasively assess AGEs in human skin, as a reflection of the systemic AGE burden in individuals. This tool assesses skin autofluorescence (SAF), using the fluorescent properties that several AGEs possess. However, a number of factors exist that influence the assessment of SAF using the AGE Reader. For example, diet, smoking status, physical activity, skin type, renal function, and chronic inflammation. Therefore, both glycaemia and other factors should be taken into account when using the AGE Reader measurement in an individual; in a clinical setting, and for decisions on clinical care. This review will address the AGE Reader as a clinical tool to assess accumulation of AGEs in the skin

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https://doi.org/10.1016/j.ymeth.2021.02.016
Received 12 October 2020; Received in revised form 16 December 2020; Accepted 21 February 2021
Available online 23 February 2021
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and different factors that potentially influence the assessment and interpretation.

### 1.1. Brief biochemistry of AGEs

The slow Maillard reaction between reducing sugars and proteins, and/or lipids is the classical mechanism of AGE formation [12]. Within a few hours, a Schiff base is formed from the interaction between carbonyl groups of reducing sugars and amino groups of proteins. More stable Amadori products are the result of intramolecular rearrangement of the Schiff base. The Amadori products undergo a slow process of oxidation which leads to reactive carbonyl compounds, precursor molecules of AGEs. Within weeks to months, this leads to the formation of AGEs [13,14]. Many different AGEs have been identified, such as pentosidine, glucosepane, Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1), Nε-carboxymethyl-lysine (CML), and Nε-carboxy-ethyl-lysine (CEL) [15].

Glycemic, dicarbonyl, and oxidative stress are the main drivers of AGE formation [13]. Besides the slow pathway of glycemic stress, AGEs form through a much faster pathway of 'dicarbonyl stress', a potentially more important route of the formation of precursor molecules of AGEs [13,16,17]. Fig. 1. Also, several exogenous sources of AGEs have been identified, such as tobacco smoke and AGEs present in nutrition [18,19].

AGEs can be harmful by forming cross-links. Long-lived proteins, like collagen, are, due to their slow turnover, susceptible to cross-link formation [20]. Cross-links affect the function of proteins, for example, they can lead to stiffening of proteins in muscles [21], tendons [22], vascular walls [23], cartilage [24], and dermis of the skin [9,25]. In 1980, Monnier and Cerami discovered and chemically characterized the occurrence of the Maillard reaction in long-lived lens proteins [20]. Moreover, Monnier et al. found significant correlations between age-adjusted collagen-linked fluorescence (CLF) and diabetic complications [26]. AGEs also have the ability to accumulate in endothelial cells and interact with fibroblasts [27,28]. While AGEs are formed under the influence of different pathways of stress, they in turn have the potential to develop and promote oxidative stress, and to induce inflammation after binding to cell surface receptors [14,29]. The receptor for advanced glycation endproducts (RAGE) is such an example.

## 2. Non-invasive assessment of skin fluorescence

AGEs can be measured in blood or tissue samples using several techniques such as enzyme linked immunosorbent assay (ELISA), fluorescence spectroscopy, and fluid chromatography and gas

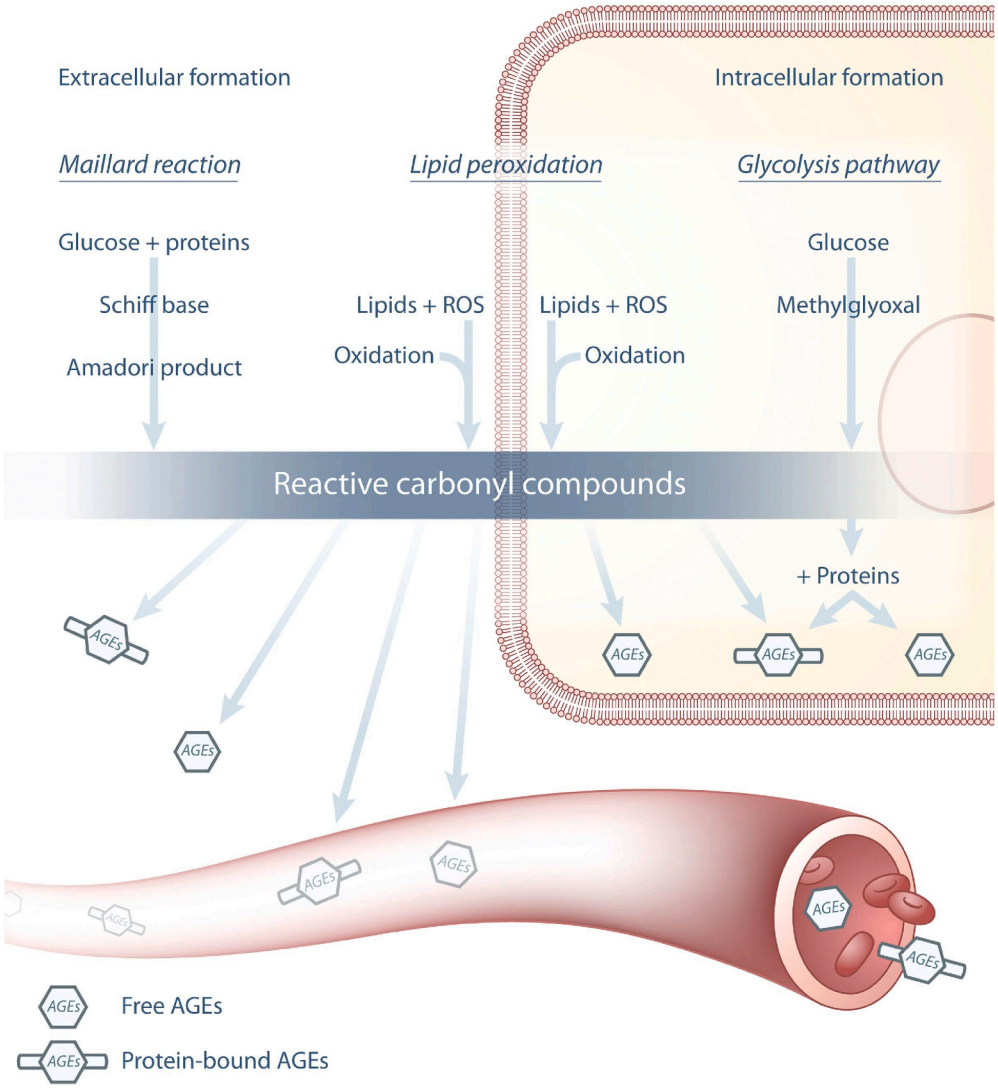


**Fig. 1. The three different pathways leading to advanced glycation endproducts (AGEs) formation.** The formation of AGEs by the Maillard reaction, lipid peroxidation, and the glycolysis pathway. ROS, reactive oxygen species. This figure has been published before and is reproduced with approval from de Vos [13].

chromatography with mass spectrometry [30,31]. However, as stated before, skin biopsies are necessary to assess long-term AGE accumulation, which is reflected in tissue. This is not feasible at study and certainly not at population level.

Skin fluorescence, emitted by several AGEs, can be measured non-invasively with different devices. CLF (excitation at 370 nm, emission at 440 nm) contributes to the fluorescence signal. Apart from the AGE Reader which we will discuss in more detail below, another device, the SCOUT (VeraLight, Inc., Albuquerque, NM, USA), also measures skin fluorescence non-invasively, referred to as skin intrinsic fluorescence (SIF). The devices differ from each other by type light and spectrum [32]. The AGE Reader SU uses a black light source with a peak wavelength of 360–370 nm for illumination and measures emission in the 420–600 nm range. The SCOUT emits light with a light emitting diode with a wavelength centered at 375 nm and fluorescence is detected at 435–655 nm [33].

Different studies have shown that skin fluorescence correlates with mean HbA1c [34,35]. This increases when HbA1c is measured over a longer period. When comparing SAF with a single measurement of HbA1c, the association with SAF is only moderate. This may depend on the short lifespan of red blood cells (8–12 weeks). Therefore, in comparison to the traditional measure HbA1c, SAF appears to be a good marker of past long-term tissue damage.

Globally, 34–47% of the variance of SAF can be statistically explained (Fig. 2) [36,37]. Age is the most important contributor, 23.8–28.5%. Other, less important contributors include lifestyle factors, such as smoking and coffee intake, explaining 3.7–8.9% and 1.6–3.6%, respectively. Physical activity, age, gender, body mass index and pack-years contributed to SAF by 25.5–35.8% in the final prediction model by van de Zande and colleagues [37]. Gender contributes less significantly, about 0.4–1.9%. Additionally, genetic factors play a role. In the Life-Lines cohort by van Waateringe et al. genetic factors explained 2.1–2.7% of the variance in SAF [36]. However, the influence of heritability is probably much higher, but this has not been studied for SAF as far as we know. For example, 28% of the interindividual variation in lens protein autofluorescence was attributable to hereditary factors, in addition to environmental factors [38].

## 3. AGE Reader

In the late 1990-s, transcapillary leakage of sodium fluorescein in skin capillaries was assessed as a marker of endothelial dysfunction in diabetes [39,40]. It was noted that prior to intravenous injection of fluorescein and its subsequent transcapillary leakage in the dermis, increased fluorescence of the skin was already present in patients with diabetes, especially in the dermal layer. This serendipitous finding initiated the development of dedicated equipment to address this increased SAF in diabetes patients in more detail.

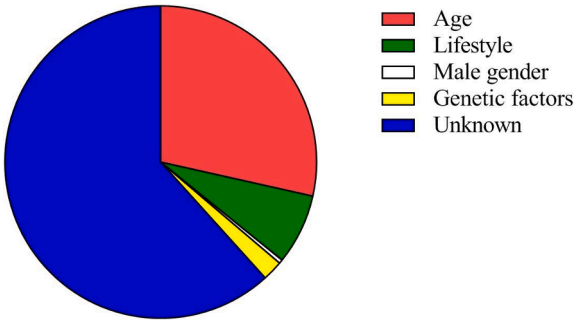


**Fig. 2. Factors influencing the AGE Reader measurement.** This pie-chart figure shows an overview of different factors contributing to the AGE Reader measurement in the general population. Since the percentual contribution of individual components largely depends on the population studied, these are general assumptions. For patients with chronic diseases such as diabetes and chronic kidney disease percentages will be different. For example, due to kidney dysfunction or hyperglycaemia. In addition, local skin factors and/or hypertension may play a role.

In 2004, a first report showed that SAF, non-invasively assessed in the skin of the forearm, was related to AGE levels in dermal biopsies in diabetes patients and in healthy controls [25]. In these dermal biopsies, obtained from the same site on which SAF was performed, several AGEs were determined using chromatographic and mass spectrometric methods. The study pointed out that SAF reflects dermal AGE levels and could be used as a biomarker in AGE-related diseases. The device used to measure SAF was developed at the University Medical Center Groningen, The Netherlands, and was later called the AGE Reader. Although the exact individual molecular structures and the diversity of (epi) dermal tissue constituents contributing to SAF are difficult to establish, the wavelength band of the AGE Reader was chosen as such that primarily fluorescent AGEs could be assessed.

Studies using the AGE Reader confirmed that patients with diabetes indeed have higher SAF levels than control groups, especially in diabetes patients with micro- or macrovascular complications [2,16,41,42]. Subsequent studies also confirmed SAF as a predictor of complications in type 2 diabetes [41,43,44].

Because of its non-invasive character, the small size of the portable AGE Reader, and its ease to perform measurements, SAF is more suitable to evaluate the role of AGEs in large scale studies and clinical practice than the laborious biochemical assessment of AGEs in tissue biopsies and plasma samples.

### 3.1. Measuring SAF using the AGE Reader

The AGE Reader SU contains an UV-A lamp that emits light with a peak wavelength of 360–370 nm. Light reflected and emitted in the 300–600 nm range from the skin is measured in this research version by an inbuilt spectrometer, using an UV glass fibre (Fig. 3). In the later, more convenient version AGE Reader mu, the spectrometer was replaced by a set of photodiodes with peak sensitivities for different wavelengths, allowing the instrument to be used stand-alone and decreasing its overall size, making practical use more easy. Before every measurement with the AGE Reader SU, dark and white reference readings are performed to, respectively, correct for background light and to calculate skin reflectance. SAF is measured on the volar side of the forearm. Care should be taken to perform this measurement in an area with normal skin with minimal sunlight exposure. Initially, SAF measurements were not considered for analysis if the UV reflectance level was <10%. After introduction of more sophisticated and validated skin color correction software (version 2.3), this limit was lowered to 6%. This adaptation potentially allowed the use of SAF in a broader group of persons with darker skin color. To correct for differences in light absorption, SAF is calculated as a ratio of emitted fluorescence (420–600 nm) to reflected excitation light (300–420 nm). Consequently, SAF is expressed in arbitrary units (AU). Intra-observer variation of repeated autofluorescence measurements is 5% to 6% within one day [25].

## 4. Validation of the AGE Reader in skin biopsies

SAF has been proven to be a valid marker of AGE accumulation in the body. This technique has been validated in skin biopsies of patients with diabetes mellitus, hemodialysis patients, and healthy controls in several studies, as summarized in Table 1.

Studies by Meerwaldt et al. [10,25] first addressed the validity of the AGE Reader as a tool to assess AGE accumulation in non-pigmented skin. They found a significant strong correlation between SAF and AGEs in skin biopsy samples of primarily white European diabetic patients (n = 46) and age- and sex-matched non-diabetic controls (n = 46). The correlation was found between SAF and the fluorescent AGE pentosidine, and also the non-fluorescent AGEs CML and CEL. Moreover, Meerwaldt

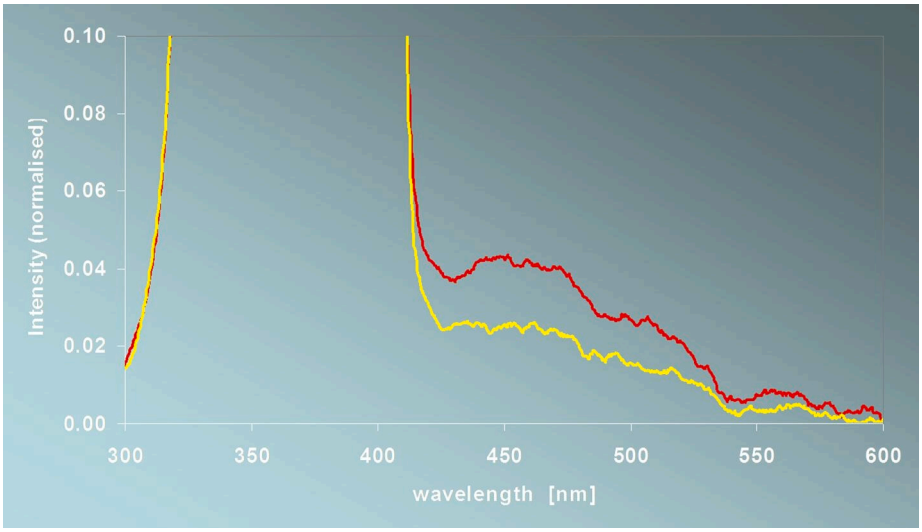


**Fig. 3. Example of normalized intensity spectra measured from the skin after excitation with UV light.** The red line represents a diabetes patient. The yellow line represents a control. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 1**
**Overview of AGE Reader validation studies and correlations between different AGEs from skin biopsies and SAF.**

| | N | CLF 370/440 nm | CML | Pentosidine | CEL |
|---|---|---|---|---|---|
| **Meerwaldt et al.** [25] | 13 diabetic type 1 patients; 18 diabetic type 2 patients, and 12 control subjects | r = 0.62** | r = 0.55** | r = 0.55** | r = 0.47** |
| **Meerwaldt et al.** [9] | 29 hemodialysis patients | r = 0.71** | r = 0.45* | r = 0.75** | r = 0.45* |
| **Hu et al.** [45] | 5 diabetic patients; 11 arteriosclerosis obliterans patients, and 17 healthy traffic-accident victims | – | Not reported | Not reported | Not reported |
| **Mulder et al.** [47] | 8 patients and 30 control subjects | r = 0.44* | r = 0.33 | r = 0.22 | r = 0.20 |

AGEs, advanced glycation endproducts; SAF, skin autofluorescence; CLF, collagen-linked fluorescence; CML, Nε-carboxymethyl-lysine; CEL, Nε-carboxy-ethyl-lysine; *Representing a significant correlation <0.05; **Representing a significant correlation <0.005.

et al. [9] found in 29 skin biopsies of hemodialysis patients a strong correlation between SAF and CLF, and pentosidine. The correlations with CML and CEL were less strong, although being significant.

A recent study by Hu et al. [45] showed in skin, artery, and nerve samples of 5 diabetic and 28 non-diabetic Chinese patients, who had encountered lower-limb amputation, that SAF was independently associated with different AGEs, including CML in skin, and pentosidine in artery and nerve. A Japanese study found that skin pentosidine content correlated significantly with SAF and bone pentosidine content. They did not find a significant correlation between SAF and pentosidine content of bone [46].

Mulder et al. showed a significant moderate correlation between SAF and CLF in 8 patients and 30 healthy young controls [47].

## 5. SAF as a predictor for chronic disease complications and mortality

In addition to its validity of measuring AGEs in skin, SAF has also been shown to have strong associations with clinical diseases. Over the last two decades, the number of clinical studies on SAF has increased exponentially. It has been clearly demonstrated that SAF is strongly associated with aging, and many chronic, age-related diseases in which the role of AGEs had been demonstrated using other modalities for AGE quantification. In that sense, the AGE Reader may be helpful in disease prevention, patient management, and research in large populations. Several studies suggested that SAF is useful as a predictor for cardiovascular events in patients with CVD [48,49], but also in diabetes patients [41,43,44,50], and in patients with chronic kidney disease [51–53]. Furthermore, a few studies showed that SAF is an independent risk factor for mortality in patients with chronic kidney disease [53,54], with diabetes type 2 [32,34], and in patients with peripheral artery disease [55]. Next to predicting complications and mortality in patients, SAF is also a predictor of incident type 2 diabetes, CVD, and mortality in the general population [56].

## 6. Endogenous skin factors that influence SAF

During its measurement, SAF is influenced by different factors in the skin, including chromophores, fluorophores, but also by epidermal thickness, which limit the specific measurement of AGE-related signs. Furthermore, SAF should be a reflection of the systemic AGE burden, and not of local structures present in the skin. Table 2 represents different chromophores and fluorophores which may interfere with the SAF measurement [57,58].

Masters et al. [59] found that two-photon microscopy at 730 nm (equivalent to 365 nm) could penetrate in human skin to a depth down to 200 μm. Epidermal thickness is a limiting factor for wavelengths <300 nm [60]. However, Sandby-Møller et al. [61] concluded that correction for epidermal thickness, representing epidermal absorption and scattering, was negligible on SAF. In contrast, Murray et al. found that SAF was lower at the distal phalanx of the fingers especially in patients with systemic sclerosis, a site where skin thickening is the greatest in these patients [62]. Most absorption of UV-A and visible light in the epidermis is due to melanin [63]. Melanin is formed by melanocytes and is found in melanosomes. Light absorption by melanin is dependent on the amount of melanosomes in the epidermis [63]. The SAF measurement with the AGE Reader is, therefore, corrected for the reflected excitation light source.

**Table 2**
**Overview of chromophores and fluorophores possibly interfering with SAF.**

| | Absorption peak (nm) | Excitation peak (nm) | Emission peak (nm) |
|---|---|---|---|
| **Chromophores** | | | |
| Melanin | Increases to shorter wavelengths | | |
| Collagen | ~290, ~320 | 325 | 400, 405 |
| Elastin | ~325 | 290, 325 | 340, 400 |
| Oxyhemoglobin | 412, 542, 577 | | |
| Deoxyhemoglobin | 430, 555, 760 | | |
| Bilirubin | 460 | | |
| **Fluorophores** | | | |
| CLF | | 328 | 378 |
| Pentosidine | | 335 | 385 |
| NADH | | 350 | 460 |
| CLF | | 370 | 440 |
| Keratin | | 370 | 460 |
| Crossline | | 379–380 | 440–463 |
| Vitamin D | | 390 | 480 |

SAF, skin autofluorescence; CLF, collagen-linked fluorescence.

In addition to the epidermis, in the dermis, several structural proteins and tissue constituents are present, such as collagen, elastin, and blood vessels that may interfere with the measurement of SAF. Hemoglobin, expressed in red blood cells, is also a major contributor to absorption of light in the UV-A and visible range, as integrated in the AGE Reader [57,60,64]. Moreover, the blood chromophore bilirubin seems to play a role on SAF, but to a lesser extent [57,60].

There are also skin fluorophores that may influence SAF, like keratin, NADH, and vitamin D [57,64]. However, earlier research of our research group showed that variance in SAF could for a major part be explained by variations in the AGE pentosidine in dermal tissue of white European subjects [64].

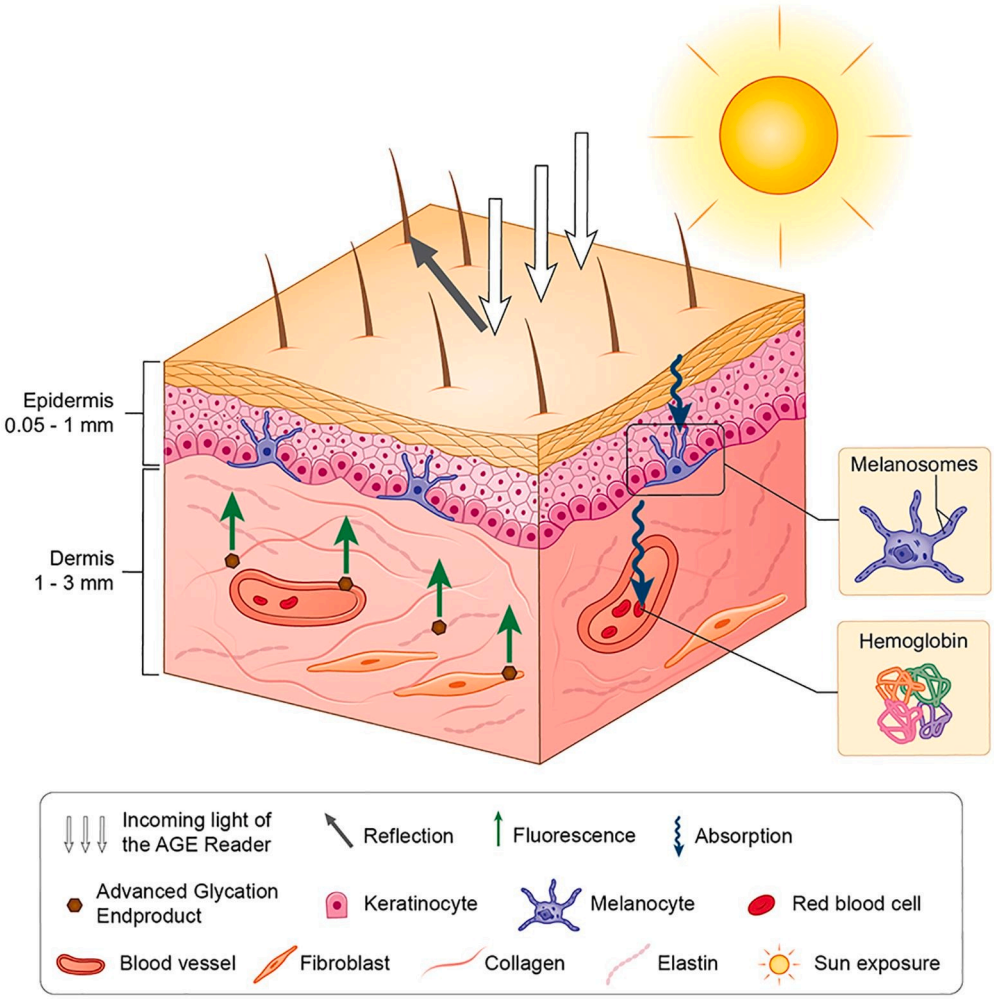


**Fig. 4. Skin autofluorescence (SAF), influencing factors, and localization of advanced glycation endproducts (AGEs).** Schematic overview of the skin. This figure shows light of the AGE Reader illuminating the skin. SAF is subsequently calculated by the ratio of skin fluorescence and reflectance. Absorption of light is mainly due to the main absorbers melanin and hemoglobin. Also, the localization of AGEs is shown.

In addition, sun exposure is of importance. Sun exposure causes melanin levels to increase. This may cause absorption of fluorescent light leading to lower SAF values. Therefore, the SAF measurement is performed on the volar side of the forearm, because this location shows minimal seasonal change in pigment. Crisan et al. [27] found that AGE accumulation, e.g. CML, is higher in sun-exposed skin compared to sun-unexposed skin. However, in a previous study in white European subjects, intra-individual seasonal variance showed an Altman error of around 6%, suggesting that the effect of seasonal variance is probably limited [25]. Although a study by Meerwaldt et al. showed also that SAF measured at the volar site of the forearm and calf correlated strongly with each other ($r = 0.98$), the calf is not a practical location to assess SAF [25]. Fig. 4 shows a summary of the above mentioned components.

Less pigmented areas, such as palmoplantar sites, seem less suitable due to the thickness and variability of the epidermal layer at these skin sites. Nevertheless, Kim et al. [65] were able to assess significantly higher SAF values of palmoplantar sites in Asian patients with type 2 diabetes complications, in comparison with those without. Differences in SAF values were not observed at non-palmoplantar sites. Although they used a different set-up, their data suggest that other sites of measurement could be explored in patients with a dark skin type.

### 6.1. SAF and skin color

SAF can only be reliably measured in subjects with skin photo type I-IV, or reflectance values above 6% [16]. It is, therefore, important to keep skin color in mind when measuring SAF with the AGE Reader. Koetsier et al. [64] reported an algorithm to correctly measure SAF in subjects with reflectance values <12%, independent of skin color, using an additional white light in which melanin was accounted for, in addition to other relevant chromophores in the skin (hemoglobin, bilirubin), since these are accepted as main absorbers. However, the SAF measurement becomes increasingly less reliable when UV reflectance falls below 6% [66], which means that >94% of the UV light is absorbed in the skin. Possibly other fluorophores, as mentioned above, could also lead to bias. Since the exclusion of dark-skinned subjects is an important limitation, studies which extend the AGE Reader functionality to subjects with skin photo type V-VI should be encouraged.

Multiple studies have been performed to assess reference SAF values for different ethnicities. Koetsier et al. [67] provided reference values of SAF for healthy white European subjects ($n = 428$). Yue et al. [68] established reference values of SAF for the Chinese population ($n = 991$). A study by Klenovics et al. [69] established reference values of SAF in healthy subjects from Slovakia ($n = 1385$). Furthermore, Ahmad et al. [70] assessed reference values of SAF in a Saudi population ($n = 1999$).

Moreover, other studies have been performed to encounter SAF in different ethnicities, with different skin reflectance values, such as in subjects from Arabic countries, South Asia, Southeast Asia, North Africa, the East of the Mediterranean sea, and Europe [66,71]. However, it is difficult to compare these studies. This is due to several factors, such as the model of the AGE Reader used, inter-individual variances in skin type, and disturbed SAF values in subjects with reflectance values between 6 and 8%.

In conclusion, when measuring SAF with the AGE Reader, skin reflectance instead of ethnicities should be taken into account since the AGE Reader is only suitable in subjects with reflectance values >6%, or skin photo type I-IV. Given that the measurement in subjects with reflectance values <6% is still unreliable, studies encountering the AGE Reader functionality in very dark-skinned subjects should be encouraged.

### 6.2. Changes in SAF due to stress and physical activity

Classically, SAF measured with the AGE Reader is considered to be a reflection of AGEs that are linked to long-lived proteins accumulated over a time period of several years to decades. However, as outlined above, SAF may also reflect the interstitial compartment of the skin and potentially its capillary network. This assumption brings into mind that SAF may also be influenced by more recent changes in AGEs. Potentially the AGE Reader could be able to measure acute rises and falls in levels of circulating AGEs, which are generally caused by oxidative stress. A cause and consequence of oxidative stress is dicarbonyl stress, leading to the formation of glyoxal and methylglyoxal [72], an example of fast formation of AGEs. The reaction of methylglyoxal with the protein arginine results in the AGE MG-H1, while CML derives from the reaction of glyoxal with lysine [73]. However, since these AGEs are not fluorescent by themselves, indirect effects of other fluorescent AGEs should be taken into account.

Acute and strenuous exercise may cause an overproduction of reactive oxygen species (ROS), which leads to higher levels of oxidative stress [74–76]. On the other hand, regular physical activity can reduce formation of ROS [74], and might, therefore, play an important role in preventing AGE accumulation. Also, acute and chronic diseases are associated with higher levels of oxidative stress [76], which plays a role in the formation of AGEs (Fig. 5). Several studies were conducted in support of this, as discussed below.

Meertens et al. [11] performed a study in ICU patients in which they found that the SAF level did not change in a period of 7 days, while plasma markers of AGEs and oxidative stress clearly increased. However, in another study, it was shown that SAF levels can fluctuate over time. Our group investigated the SAF level in ST-elevation myocardial infarction (STEMI) patients and controls [48]. STEMI patients had a significantly higher SAF level compared to controls. When SAF was measured >200 days after STEMI a significant decrease was seen in the STEMI patients, however, SAF remained higher compared to the control group. The rise in SAF might be caused by oxidative stress related to an acute STEMI. Pol et al. [77] found a significant increase of SAF after colorectal surgery, and this was related to markers of surgical stress (blood loss and duration of operation). They also assessed SAF 30 days after the surgery and showed that SAF was decreased within approximately four days to nearly the same level as before the surgery. However, SAF remained higher or even increased after the surgery when there were complications. The authors suggested that SAF might provide information of the condition of the patient before and after surgery.

Other studies investigated the relation between AGEs, instead of SAF, and physical activity over a period of time [78–82]. Almost all studies indicated that physical activity decreases AGE levels in the body. There are also cross-sectional studies that investigated the relationship between SAF or AGE levels and physical activity. Different studies found an inverse relation between physical activity and SAF [69,83–85]. These cross-sectional studies have in common that SAF decreases with increased levels of regular physical activity. On the contrary, Kellow et al. [86], Sanchez et al. [87], and Hansen et al. [88] did not find a relationship between physical activity and SAF. No studies investigated the direct effect of physical activity on SAF.

### 6.3. Changes in SAF due to nutrition

SAF may be directly influenced by nutritional intake of AGE-rich meals, as demonstrated in studies from the group of Vlassara [89]. Kellow et al. [86] found a positive correlation between SAF and intake of meat/meat products ($r = 0.22$). Sanchez et al. [87] reported that adherence to a Mediterranean diet was inversely associated with SAF. Moreover, cooking methods that utilise high temperature and low moisture increase the AGE content of food above the uncooked state [19]. To the best of our knowledge, no studies exist which investigate the influence of cooking methods on SAF. Although, Uribarri et al. [19] included the impact of cooking methods on AGE levels in foods. Studies on its influence on SAF should be encouraged since exogenous sources, such as coffee intake and smoking, seem to influence the SAF measurement. These are, however, effects on the long-term and the direct effect has not been studied. Stirban et al. [90] reported that SAF

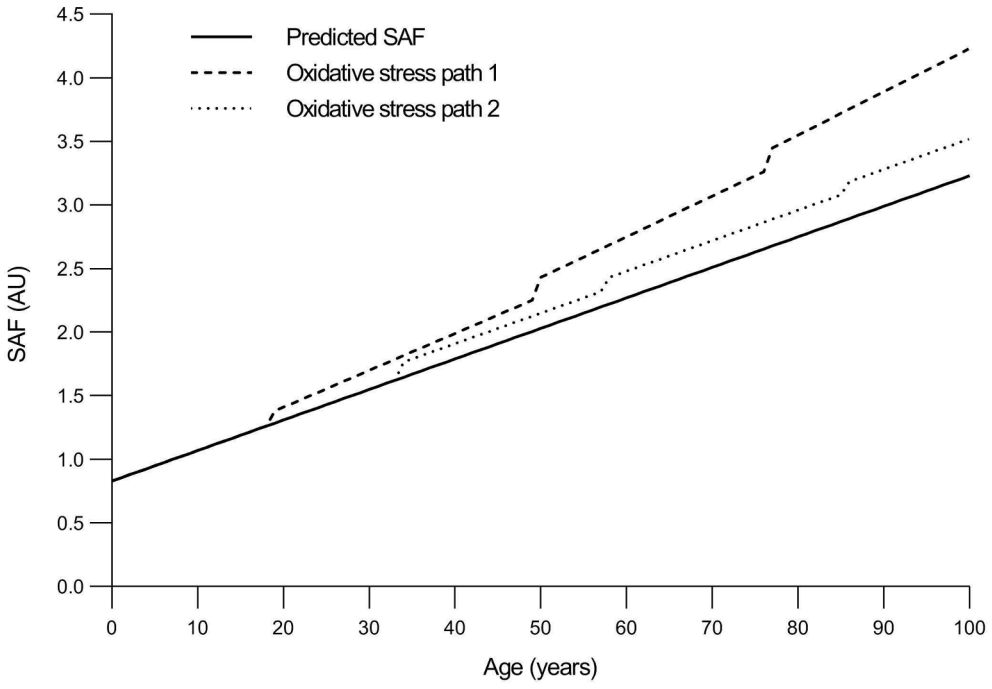


**Fig. 5. Schematic presentation showing a suggested increase in skin autofluorescence (SAF) caused by age and disease episodes.** During a disease episode levels of oxidative stress are increased. These higher levels of oxidative stress might cause an increase in SAF in addition to the gradual influence of age. The black line represents the general increase in SAF over the years based on the article of Koetsier et al. [67]. SAF = 0,024 * age in years + 0,83. The dotted lines represent a trajectory with episodes of increased oxidative stress. Since the exact effect of oxidative stress on SAF is unknown, the data are created using fictional data. Oxidative stress path 1 is an example of an increased oxidative stress level for a longer period (e.g. due to diabetes). Therefore, the SAF will increase more per year compared to the general increase in SAF. As a result, the line has a steeper slope. Oxidative stress path 2 is an example of a temporary increase of oxidative stress. Thereafter, the oxidative stress level will decrease and continue with the same slope as the general increase in SAF.

increased two hours postprandially. In addition, Botros et al. [91] found that SAF was associated with coffee intake. An extensive discussion on the influence of diet on AGE levels is beyond the scope of this review.

## 7. Exogenous skin factors that influence SAF

The SAF measurement is influenced by different skin care products. A study by Noordzij et al. [92] showed that SAF is affected by body lotion (SAF increase of 18%), day cream (increase of >100%), sunscreen (increase of >100%), and self-browning cream (increase of >100%). Vasoconstriction, induced by a cold bath, caused a SAF increase of 10% [92]. Vasodilatation, caused by a hot bath and capsicum cream, gave a SAF decrease of, respectively, 18% and 22% [92]. SAF did not return to baseline values after cleaning with alcohol swabs and subsequent washing with soap, except for body lotion.

The effect of self-browning cream and sunscreen on SAF persisted for 2 weeks and 4 days, respectively. However, this was only assessed in three subjects [92]. This is in accordance with Ahmad et al. [70], who found in a pilot study with nine subjects that the effect of skin lotion on SAF is partially reduced (62%) by skin rinsing with soap and water. Therefore, the use of skin care products should be verified previous to performing the AGE Reader measurement. If used, dependent on the type of product, the measurement should be cancelled or postponed.

## 8. Conclusion

SAF has been proven to be a valid marker of AGE accumulation in the body. Various studies showed that SAF is a predictor of cardiovascular events and risk factor for mortality in patients with CVD, diabetes mellitus, chronic kidney disease, and peripheral artery disease. Importantly, SAF does also seem to be a predictor of incident type 2 diabetes, CVD, and mortality in the general population.

However, many different components exist which may influence the AGE Reader measurement. The possible influence of endogenous components and exogenous components have been discussed. Since SAF did not always return to baseline values after cleansing, use of skin care products should be taken into account.

Moreover, given that the SAF measurement is only reliable in subjects with skin reflectance values >6%, it is of importance to keep this reflectance value in mind. To encounter the current contraindications of the SAF measurement, studies focusing on, for example, eliminating the influence of the use of creams and skin reflectance, should be encouraged.

Since the SAF measurement penetrates into the dermis, changes of plasma AGEs or their accumulation in the interstitial space may be detected, and, therefore, acute changes of AGEs may also be detected. Indeed, different situations, such as acute diseases and strenuous physical exercise, showed changes in levels of SAF. However, more research needs to be performed to better understand the role of different AGEs and SAF, and the association with different types and amounts of physical activity.

## Disclosures

A.J. Smit is founder and shareholder of DiagnOptics Technologies BV, The Netherlands, manufacturing autofluorescence readers (www.diagnoptics.com).

## CRediT authorship contribution statement

**I.M. Atzeni:** Conceptualization, Writing - original draft, Visualization. **S.C. van de Zande:** Conceptualization, Writing - original draft, Visualization. **J. Westra:** Conceptualization, Writing - review & editing, Supervision. **J. Zwerver:** Conceptualization, Writing - review & editing, Supervision. **A.J. Smit:** Conceptualization, Writing - review & editing, Supervision. **D.J. Mulder:** Conceptualization, Writing - review & editing, Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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