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Review

# Evaluation of tissue accumulation levels of advanced glycation end products by skin autofluorescence: A novel marker of vascular complications in high-risk patients for cardiovascular disease

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ABSTRACT

A non-enzymatic reaction between reducing sugars and the amino groups of proteins, lipids and nucleic acids is known as the "Maillard reaction". The reactions have progressed in a normal aging process and at an accelerated rate under hyperglycemic, inflammatory, and/or oxidative stress conditions, thus leading to the formation and accumulation of advanced glycation end products (AGEs). Cross-linking modification of organic matrix proteins such as collagen by AGEs not only leads to an increase in vascular and myocardial stiffness, but also deteriorates structural integrity and physiological function of multiple organ systems. Furthermore, there is a growing body of evidence that interaction of AGEs with a cell surface receptor RAGE elicits oxidative stress generation and subsequently evokes inflammatory, thrombogenic and fibrotic reactions, thereby being involved in the development and progression of various age- or diabetes-related disorders, including cardiovascular disease (CVD), Alzheimer's disease, osteoporosis, cancer growth and metastasis. Skin AGE levels measured in biopsy specimens are associated with the development and progression of diabetic microangiopathy. Recently, accumulation levels of AGEs in the skin can be measured non-invasively by autofluorescence. Accumulating evidence has suggested that skin autofluorescence (SAF) is correlated with the presence and severity of vascular complications of diabetes and could predict future cardiovascular events and death in patients with diabetes. This review summarizes the pathophysiological role of tissue accumulation levels of AGEs in vascular damage in high-risk patients, especially focusing on the association between SAF and cardiorenal disorder.



## 1. Introduction

Sugars, including glucose and fructose, can react non-enzymatically with the amino groups of proteins, lipids and nucleic acids to form reversible Schiff bases, and then Amadori products [1,2]. These early glycation products undergo further complex reactions such as rearrangement, dehydration and condensation to become irreversibly cross-linked, heterogeneous fluorescent derivatives called "advanced glycation end products (AGEs)" [1,2]. The process of non-enzymatic glycation is also known as the "Maillard reaction", and formation and accumulation of AGEs in various tissues have progressed at a physiological normal aging and at an extremely accelerated rate under hyperglycemic, inflammatory, and/or oxidative stress conditions [1,2]. The pathological role of the non-enzymatic modification of proteins by reducing sugars has become increasingly evident in numerous types of diseases [2–10]. Indeed, non-enzymatic glycation and cross-linking of proteins not only lead to an increase in vascular and myocardial stiffness, but also deteriorate structural integrity and physiological function of multiple organ systems [2]. Furthermore, there is a growing body of evidence that interaction of AGEs with a cell surface receptor RAGE elicits oxidative stress generation and subsequently evokes inflammatory, thrombogenic and fibrotic reactions in a variety of cells, thereby being involved in diabetes- and/or age-related disorders such as atherosclerotic cardiovascular disease (CVD), diabetic microvascular complications, Alzheimer's disease, osteoporosis, and cancer growth and metastasis [2–10].

A large number of papers have shown that circulating levels of AGEs are elevated under inflammatory and/or diabetic conditions and associated with endothelial dysfunction, atherosclerotic plaque instability, impaired endothelial cell repair, vascular stiffness, insulin resistance, diabetic vascular complications and atherosclerotic CVD [2,11–17]. Moreover, skin AGE levels measured in biopsy specimens were associated with the development and progression of diabetic microangiopathy [18,19]. Recently, accumulation levels of AGEs in the skin can be measured non-invasively by autofluorescence [20]. Skin autofluorescence (SAF) is defined as the ratio of average autofluorescence over the entire 420–600 nm emission spectrum to that over 300–420 nm

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[20]. It was correlated with skin levels of AGEs such as pentosidine, N-(carboxymethyl)lysine and N-(carboxyethyl)lysine, and positively associated with age, diabetes duration, and mean glycated hemoglobin of the previous year in both type 1 and type 2 diabetic patients [20]. Accumulating evidence has shown that SAF is correlated with the presence and severity of vascular complications of diabetes and could predict future cardiovascular events and death in patients with diabetes [21,22]. These observations suggest that SAF is a reliable clinical tool for evaluating tissue accumulation levels of AGEs, whose value is a novel marker that could predict future vascular events in diabetes. This review summarizes the pathophysiological role of tissue accumulation levels of AGEs in vascular damage in high-risk patients, especially focusing on the association between SAF and cardiorenal disorder. In this review, literature searches were undertaken in Medline by the PubMed interface. Non-English language articles were excluded. Key words (SAF and (diabetes or glycation or glycosylation) and (vascular or renal)) have been used to select the articles.

## 2. Method of SAF measurement

Fig. 1A shows TrūAge Scanner™ (Morinda, Orem, UT, USA), which measures SAF that occurs from some AGEs with fluorescent properties. It can measure skin accumulation levels of AGEs non-invasively in less than 15 s. AGE measurement can be performed directly on intact healthy skin on the inner side of the lower forearm. First, turn the scanner on by pressing the power button. Then subject's forearm should be placed on the scanner as indicated in Fig. 1B. After entering the subject's age, measurement of SAF is started by pressing the confirm button (Fig. 1C). TrūAge Scanner™ advances to the measurement report screen (Fig. 1D).

### 2.1. SAF and CVD

#### 2.1.1. Vascular stiffness

Arterial stiffness is associated with the prevalence of CVD and could predict future cardiovascular events in healthy subjects and high-risk patients for CVD [2]. Extracellular matrix within the arterial wall is mainly composed of type I collagen, type III collagen and elastin [2]. Quantitative and qualitative alterations of collagens and elastin are induced by AGE-modification, which could contribute to decreased elastic properties of the vessels, thereby playing a role in arterial stiffness [2].

After adjustment for classical cardiovascular risk factors, SAF, but not serum levels of N-(carboxymethyl)lysine was independently associated with arterial stiffness evaluated by aortic pulse wave velocity in type 1 diabetic patients without clinical cardiovascular events [23]. Small and large artery elasticity was inversely, whereas systemic vascular resistance positively associated with SAF in subjects with type 1 diabetes [24]. SAF was also correlated with corneal and lens autofluorescence, C-reactive protein and circulating AGE levels, and its value was significantly higher in diabetic patients with complications compared to those without complications [24]. Furthermore, a significant association was observed between pulse wave velocity and SAF in non-diabetic group aged <65 years, but not aged ≥65 years [25], although the positive association was lost after further adjustments for age and other coronary risk factors [25]. In addition, pulse wave velocity was significantly and positively associated with SAF in patients with end-stage renal disease, which was independent of other covariates including age [26]. Dialysis modality could affect the value of SAF; SAF and aortic stiffness were higher in peritoneal dialysis compared with hemodialysis patients [27]. However, independent of dialysis modality, there was a positive association among SAF, aortic stiffness, and enhanced wave reflection in end-stage renal disease patients [27]. SAF and vessel stiffness measured by pulse wave velocity were also linked to AGEs contained in residual bypass graft material, thus being a useful marker of vessel AGE modifications in patients with coronary heart disease [28].

#### 2.1.2. Diastolic dysfunction and heart failure

Cross-linking modification of matrix proteins by AGEs is involved in myocardial stiffness as well [2]. Furthermore, engagement of RAGE with AGEs causes endothelial dysfunction and impairs myocardial calcium uptake, which in concert could lead to the development and progression of chronic heart failure.

SAF was higher in diabetic heart failure patients compared with non-diabetic heart failure subjects, and there was a correlation between SAF and diastolic dysfunction in these subjects [29]. Aerobic capacity evaluated by peak oxygen uptake on cardiopulmonary exercise testing was significantly lower in diabetic patients with heart failure, whose value was correlated with SAF, independent of age, diabetes, left ventricular ejection fractions, and New York Heart Association functional class [29]. Hartog et al. reported that SAF, but not plasma pentosidine, N-(carboxymethyl)lysine or N-(carboxyethyl)lysine, was significantly associated with diastolic dysfunction in dialysis patients [30]. Furthermore, hypertensive patients with lower SAF at baseline showed a larger improvement in diastolic function in response to anti-hypertensive treatments compared with those with higher SAF [31]. These findings support the concept that tissue accumulation of AGEs could partly explain the increased prevalence of diastolic dysfunction and heart failure in high-risk patients such as diabetes, end-stage renal disease and hypertension.

#### 2.1.3. Inflammation and oxidative stress

There is an accumulating body of evidence, ranging from cell culture experiments to pathologic analysis to epidemiologic clinical studies, that atherosclerosis is intrinsically an inflammatory disease [32]. Further, recent prospective studies have shown that higher levels of soluble form of RAGE (sRAGE) are associated with incident of cardiovascular disease or all-cause mortality in subjects with both type 1 and type 2 diabetes [33–35].

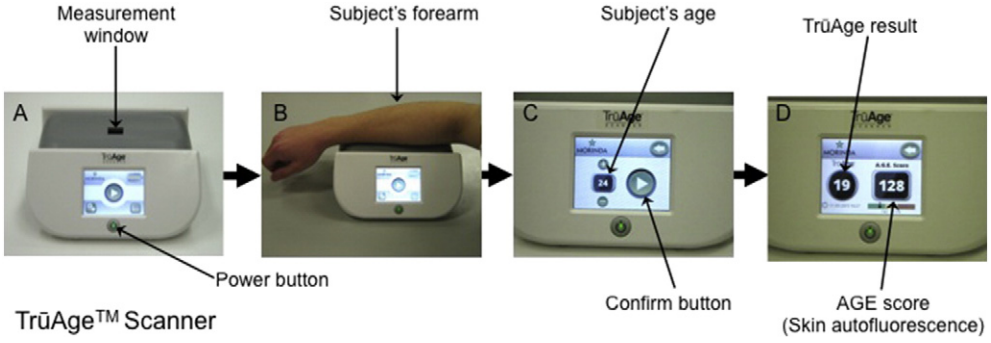


**Fig. 1.** TrūAge Scanner™. First, turn the scanner on by pressing the power button (Fig. 1A). Then subject's forearm should be placed on the scanner as indicated in Fig. 1B. After entering the subject's age, measurement of SAF should be started by pressing the confirm button (Fig. 1C). TrūAge Scanner™ advances to the measurement report screen (Fig. 1D).