Research Article

Autofluorescence of Skin Advanced Glycation End Products: Marker of Metabolic Memory in Elderly Population

Kalina Rajaobelina,1,2 Audrey Cougnard-Gregoire,1,2 Cecile Delcourt,1,2 Henri Gin,3 Pascale Barberger-Gateau,1,2 and Vincent Rigalleau1,2,3

1INSERM (Institut National de la Santé et de la Recherche Médicale), ISPED (Institut de Santé Publique d’Épidémiologie et de Développement), Centre INSERM U897-Epidemiologie-Biostatistique, Bordeaux, France. 2University of Bordeaux, France. 3Department of Nutrition-Diabetology, Haut-Lévêque Hospital, Pessac, France.

Address correspondence to Kalina Rajaobelina, MSPH, INSERM (Institut National de la Santé et de la Recherche Médicale) U 897, University of Bordeaux, 146 rue Léo Saignat, CS61292, 33 076 Bordeaux Cedex, F-33000 Bordeaux, France. Email: kalina.rajaobelina@isped.fr

Abstract

Background: Advanced glycation end products are involved in the vascular complications of diabetes, in chronic kidney disease, and in the aging process. Their accumulation in the elderly people, as reflected by skin autofluorescence (sAF), may be a marker of metabolic memory. We aimed to examine the association of sAF with glycemic and renal status 10 years earlier in older persons.

Methods: In retrospective cohort study, 328 elderly community dwellers aged of 75 years and over had sAF measurement 10 years after their inclusion in the Three-City cohort. Fasting plasma glucose and serum creatinine were measured at baseline and at 10-year follow-up. In 125 participants, HbA1c was available at these two times. Associations between sAF and the glycemic and renal status 10 years before were analyzed by multivariate linear regression adjusted for age, sex, hypertension, body mass index, hypertriglyceridemia, and smoking.

Results: Participants were 82.4 (standard deviation = 4.1) years on average, and their mean sAF was 2.8 (standard deviation = 0.7) arbitrary units (AU). After adjustment, sAF was higher in participants with long-standing diabetes (+0.38 AU, p = .01) or chronic kidney disease (+0.29 AU, p = .02) compared with healthy participants. sAF was related to fasting plasma glucose (+1 mmol/L associated with +0.08 AU, p = .01) and HbA1c (+1% associated with +0.15 AU, p = .03) 10 years earlier, but not to the current fasting plasma glucose (p = .82) and HbA1c (p = .32). sAF was also related to the distal and current estimated glomerular filtration rates (p = .002 and .004, respectively).

Conclusions: sAF reflects glycemic and renal status 10 years before, supporting its value as a marker of metabolic memory in the elderly people.

Key Words: Advanced glycation end products—Skin autofluorescence—Metabolic memory—Aging.

Received September 4, 2014; Accepted December 5, 2014.

Decision Editor: Stephen Kritchevsky, PhD

“Metabolic memory” refers to exposure to a poor metabolic environment (mainly hyperglycemic) in the past, with risk of later vascular complications despite metabolic improvement (1,2). Advanced glycation end products (AGEs) are involved in the vascular complications of...
diabetes (1), but their serum concentrations are not constantly high in people with diabetes or vascular diseases (3). AGEs formation is a slow irreversible modification of proteins. Hence, they accumulate mainly in tissues containing long life-time proteins: Half-life of skin collagen is 15 years (4). There is a growing interest in this accumulation of AGEs that can be noninvasively assessed in the skin, based on their fluorescence. Indeed, the skin autofluorescence (sAF) of AGEs correlates with concentrations of glycated collagen, pentosidine, and CML (carboxymethyl-lysine) in skin biopsies (5). AGEs in the skin are associated with vascular complications of diabetes (6). This accumulation of AGEs measured by sAF is considered as a marker of metabolic memory, yet this remains to be demonstrated. As AGEs accumulate with age (7), their deposit should be especially detectable in elderly people.

Although other mechanisms like oxidative stress, activation of protein kinase C, polyols, and hexosamine pathways can contribute to the metabolic memory of past hyperglycemia, the important role of AGEs has been emphasized in several studies (1,2). In chronic kidney disease (CKD), oxidative stress, carbonyl stress, less detoxification, and reduced renal clearance lead to more accumulation of AGEs (8). Genetics may also be linked to the sAF (9). Through inflammation and tissue damages, long-term deposit of AGEs contributes to the decline of multiple organ systems in the aging process (7). However, in the general elderly population, where diabetes and CKD are common (10), measurements of sAF have rarely been reported, and it is unknown whether sAF relates to the glucose control and/or renal function of the previous years, as a marker of long-term metabolic memory.

The objective of this population-based study was to examine whether sAF was associated with glycemic status and renal function 10 years earlier in elderly community dwellers from the Three-City (3C)-Bordeaux cohort.

Methods
Study Population
This study is based on a subsample of the Bordeaux sample of the 3C study, a multicenter cohort of noninstitutionalized participants greater or equal to 65 years at baseline in Bordeaux (n = 2,104), Dijon (n = 4,931), and Montpellier (n = 2,259), France. The aim of 3C was to estimate the risk of dementia attributable to vascular factors. Details of the study have been described elsewhere (11). All participants gave their written informed consent. Data were collected using standardized questionnaires administered during face-to-face interviews at baseline and at four follow-up examinations performed at 2, 4, 7, and 10 years after the baseline. The 3C study has been approved by the Consultative Committee for the Protection of Persons participating in Biomedical Research of the Kremlin-Bicêtre University Hospital (Paris). This study is based on baseline and 10-year follow-up. At these time points, data collection included socio-demographic characteristics, measurement of blood pressure, height, and weight. Blood samples were drawn for measurement of glycemia and serum creatinine at both times.

Among 1,214 participants in Bordeaux at 10-year follow-up of the 3C study, sAF was measured in 468 participants who accepted to participate to a hospital examination in the frame of the ALIENOR (Antioxidants, Lipides Essentiels, Nutrition et maladies Oculaires) ancillary study of 3C (12). We excluded six outliers participants who had CKD at baseline (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²) and no CKD 10 years later (eGFR ≥60 mL/min/1.73 m² at follow-up); Their first eGFR was presumably underestimated due to a transiently altered hydration status. Blood sample and determination of serum creatinine were available for 427 participants. Among them, 414 individuals had determination of fasting plasma glucose at baseline (13 were nonfasting). Moreover, 328 participants also had determination of fasting plasma glucose and serum creatinine at 10-year follow-up. In this sample, HbA1c measurement was also available for 125 participants.

sAF Measurement
Measurement of sAF has been carried out in 2009–2011 at the 10-year follow-up of 3C at Bordeaux University Hospital. The accumulation of AGEs was estimated with sAF measured by the AGE Reader (DiagnOpticsTechnologies B.V., Groningen, Netherlands) and expressed in arbitrary units (AU) (5). Measurement was performed in triplicate at the skin site on the forearm. Participants with Fitzpatrick skin phototype V and VI were not evaluated due to their skin pigmentation with ultraviolet reflectance less than 10%.

Diagnosis and Duration of Diabetes
At baseline and at the 10-year follow-up, we distinguished participants with diabetes (fasting plasma glucose ≥ 7 mmol/L or antidiabetic medication), impaired fasting plasma glucose (6.1 mmol/L ≤ fasting plasma glucose < 7 mmol/L and no antidiabetic medication) and without impaired glucose metabolism (fasting plasma glucose < 6.1 mmol/L and no antidiabetic medication) according to World Health Organization criteria (13).

During the follow-up, diabetes was considered as “absent” if participants did not have diabetes at baseline and at 10 years, “recent” if they had diabetes only at 10 year, and “longstanding” if diabetes was present at both baseline and at 10 years.

Diagnosis and Duration of CKD
eGFR was estimated using the modification of diet in renal disease study equation, and CKD was defined as a value of eGFR < 60 mL/min/1.73 m² (14).

During the follow-up, CKD was considered as “absent” if participants did not have CKD at baseline and at 10-year follow-up, “recent” if they had CKD only at 10 years, and “longstanding” if it was present at both baseline and 10 years.

Other Variables
Age, sex, body mass index (body weight/height² [kg/m²]), and other potential confounding factors were considered at baseline: hypertension (if ≥140/90 mm Hg or antihypertensive medication), hypercholesterolemia (if ≥6.20 mmol/L, or cholesterol-lowering medication), hypertriglyceridemia (if ≥1.7 mmol/L), and smoking habits.

Statistical Analysis
We described distribution of sAF according to the characteristics of the sample (Student’s t test or analysis of variance depending on number of variable’s classes).

As sAF is a continuous variable, a linear regression model was used to study the relations of interest with sAF at 10 years as dependent variable. In addition to age, sex, and smoking, which were forced in the models, we introduced the other metabolic confounding variables in multivariate models if they were associated with sAF and diabetes or CKD during follow-up at p < .20. For each analysis, we performed a first model (Model 1) adjusted on age and sex and a second model (Model 2), where we added the other metabolic confounding variables.

We first analyzed the relationship between duration of diabetes and CKD as explanatory variables and sAF as dependent variable in a single model. Absence of diabetes and CKD was considered
In a second analysis, we studied the relation between glycemia and eGFR measured at baseline and at 10 years as continuous explanatory variables and sAF at 10 years as dependent variable. Finally, the same analysis was conducted for relation between HbA1c and eGFR measured at both times and sAF. Analysis of these relationships was performed in separate models at baseline and at 10 years because of strong correlation between variables at these two times. A sensitivity analysis was realized with variables at baseline and 10 years in the same model to examine effect of collinearity.

All analyses were performed with SAS Statistical Package release 9.3 (SAS Institute, Cary, NC) and a p-value of less than .05 was considered significant.

### Results

As shown in Table 1, the study sample included 328 participants, among whom 201 (61.3%) were women. At 10-year follow-up, the mean age of the sample was 82.4 (standard deviation [SD] = 4.1) years, and mean sAF was 2.8 (SD = 0.7) AU. Between baseline and 10 years, proportion of participants with diabetes increased from 5.8% to 14.0% and proportion of participants with CKD increased from 10.4% to 41.2%. There were 19 (5.8%) participants with longstanding diabetes and 27 (8.2%) with recent diabetes. Concerning CKD, 34 (10.4%) were longstanding and 103 (31.4%) were recent. Among participants with hypertension, 66 (27.3%) used drugs of the renin angiotensin system at baseline and 135 (41.2%) at 10-year follow-up. Among the 125 participants with HbA1c measurements, the mean age was 82.1 (SD = 4.2) years and mean sAF was 2.9 (SD = 0.7) AU, similar to the whole population. At 10-year follow-up, prevalence of diabetes increased from 15.2% to 26.4%, mean HbA1c increased from 5.9% to 6.3%, and mean eGFR has declined by 10 mL/min/1.73 m².

### Table 1. sAF at 10-Year Follow-Up According to Characteristics at Baseline and at 10 Years (N = 328)

<table>
<thead>
<tr>
<th>Characteristics at Baseline</th>
<th>n</th>
<th>sAF at Year 10, Mean (SD)</th>
<th>p</th>
<th>Characteristics at Year 10</th>
<th>n</th>
<th>sAF at Year 10, Mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–79</td>
<td>108</td>
<td>2.76 (0.61)</td>
<td>.76</td>
<td>80–84</td>
<td>134</td>
<td>2.82 (0.64)</td>
<td>.01</td>
</tr>
<tr>
<td>≥85</td>
<td>86</td>
<td>2.78 (0.73)</td>
<td></td>
<td></td>
<td>201</td>
<td>2.71 (0.58)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>201</td>
<td>2.71 (0.58)</td>
<td></td>
<td>127</td>
<td>2.89 (0.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>201</td>
<td>2.71 (0.58)</td>
<td></td>
<td></td>
<td>127</td>
<td>2.89 (0.73)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>127</td>
<td>2.89 (0.73)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>292</td>
<td>3.03 (0.71)</td>
<td>.003</td>
<td>174</td>
<td>2.98 (0.66)</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>292</td>
<td>3.03 (0.71)</td>
<td></td>
<td></td>
<td>174</td>
<td>2.98 (0.66)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>17</td>
<td>3.21 (0.80)</td>
<td></td>
<td></td>
<td>17</td>
<td>3.21 (0.80)</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease†</td>
<td></td>
<td></td>
<td>.07</td>
<td></td>
<td></td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>No</td>
<td>294</td>
<td>2.76 (0.65)</td>
<td></td>
<td>191</td>
<td>2.70 (0.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34</td>
<td>2.98 (0.66)</td>
<td></td>
<td>137</td>
<td>2.89 (0.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension‡</td>
<td></td>
<td></td>
<td>.08</td>
<td></td>
<td></td>
<td></td>
<td>.15</td>
</tr>
<tr>
<td>No</td>
<td>86</td>
<td>2.68 (0.66)</td>
<td></td>
<td>56</td>
<td>2.67 (0.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>242</td>
<td>2.82 (0.65)</td>
<td></td>
<td>265</td>
<td>2.89 (0.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia§</td>
<td></td>
<td></td>
<td>.22</td>
<td></td>
<td></td>
<td></td>
<td>.70</td>
</tr>
<tr>
<td>No</td>
<td>136</td>
<td>2.84 (0.63)</td>
<td></td>
<td>137</td>
<td>2.80 (0.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>192</td>
<td>2.74 (0.67)</td>
<td></td>
<td>191</td>
<td>2.77 (0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td>.02</td>
<td></td>
<td></td>
<td></td>
<td>.19</td>
</tr>
<tr>
<td>&lt;25</td>
<td>131</td>
<td>2.69 (0.59)</td>
<td></td>
<td>154</td>
<td>2.71 (0.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–30</td>
<td>144</td>
<td>2.79 (0.67)</td>
<td></td>
<td>130</td>
<td>2.83 (0.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>53</td>
<td>2.99 (0.71)</td>
<td></td>
<td>44</td>
<td>2.88 (0.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia¶</td>
<td></td>
<td></td>
<td>.05</td>
<td></td>
<td></td>
<td></td>
<td>.42</td>
</tr>
<tr>
<td>No</td>
<td>280</td>
<td>2.75 (0.64)</td>
<td></td>
<td>65</td>
<td>2.77 (0.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>48</td>
<td>2.95 (0.73)</td>
<td></td>
<td>263</td>
<td>2.84 (0.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td>.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>212</td>
<td>2.73 (0.59)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>99</td>
<td>2.85 (0.76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>17</td>
<td>3.08 (0.70)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: sAF = skin autofluorescence; SD = standard deviation.

*No diabetes: fasting plasma glucose < 6.1 mmol/L and no antidiabetic medication. Impaired fasting plasma glucose: 6.1 mmol/L ≤ fasting plasma glucose < 7 mmol/L. Diabetes: fasting plasma glucose ≥ 7 mmol/L or antidiabetic medication.

†eGFR < 60 mL/min/1.73 m².

‡Systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or antihypertensive medication.

§Plasma total cholesterol ≥ 6.20 mmol/L or cholesterol-lowering medication.

¶Plasma triglycerides ≥ 1.7 mmol/L.

as reference. In a second analysis, we studied the relation between glycemia and eGFR measured at baseline and at 10 years as continuous explanatory variables and sAF at 10 years as dependent variable. Finally, the same analysis was conducted for relation between HbA1c and eGFR measured at both times and sAF. Analysis of these relationships was performed in separate models at baseline and at 10 years because of strong correlation between variables at these two times. A sensitivity analysis was realized with variables at baseline and 10 years in the same model to examine effect of collinearity.

All analyses were performed with SAS Statistical Package release 9.3 (SAS Institute, Cary, NC) and a p-value of less than .05 was considered significant.
without, with recent, and with long-standing diabetes, respectively (Supplementary Table). In the same way, sAF was 2.7 (SD = 0.7), 2.9 (SD = 0.6), and 3.0 (SD = 0.7, p = .03) for participants without CKD, with recent CKD, and with long-standing CKD, respectively. sAF values at 10 years were significantly associated with diabetes at baseline (p = .003) and with borderline significance, with CKD at baseline (p = .07); they were higher in men (Table 1). sAF also increased with body mass index and hypertriglyceridemia at baseline with borderline significance and was higher in people who had ever smoked (former or current) at baseline. At 10 years, only current diabetes and CKD were significantly associated with higher sAF. sAF did not differ according to use of drugs of the renin angiotensin system. At baseline, mean sAF was 2.79 (SD = 0.65) in users versus 2.75 (SD = 0.67) in nonusers (p = .61). At 10 years, mean sAF was 2.78 (SD = 2.69) versus 2.79 (SD = 2.67, p = .95).

**Duration of Diabetes and CKD and sAF**

The relationships between sAF and duration of diabetes and CKD are shown in Table 2. Only long-standing diabetes (vs no diabetes) and long-standing CKD (vs no CKD) were significantly associated to higher sAF at 10-year follow-up. Adjusted for age and sex, sAF was higher by 0.42 AU (95% confidence interval [95% CI] = 0.12; 0.42) in long-standing diabetes and by 0.32 AU (95% CI = 0.08; 0.55) in long-standing CKD. These associations remained significant after adjustment for other confounding variables. Nonsignificant intermediate values were found for recent diabetes and CKD.

**sAF and Glycemia, HbA1c and eGFR at 10Years and at Baseline 10Years Before**

As shown in Table 3, sAF was associated to the eGFR, but not to the glycemia at 10 years, whereas it was related to both parameters 10 years before: a glycemia higher of 1 mmol/L at baseline was significantly associated to higher sAF of 0.07 AU at 10 years. In the sensitivity analysis, we introduced in the same model variables at baseline and at 10-year follow-up. For glycemia, the same results was found, but for eGFR, results lost significance, probably because of loss of power due to strong collinearity between variables at baseline and at 10 years. This association between sAF and glycemia at baseline was not significant in the patients without diabetes 10 years before (p = .46, n = 309), whereas the association between sAF and eGFR at 10 years before was still significant, when limited to participants without CKD 10 years before (β = −0.007, p = .02, n = 294). At baseline, in the 125 participants with HbA1c measurements, the same association as with glycemia and eGFR was observed. Higher HbA1c of 1% and a lower eGFR of 10 mL/min/1.73 m² 10 years ago were respectively associated with an increase of 0.15 AU (95% CI = 0.02, 0.28) and 0.10 AU (95% CI = 0.01, 0.16) of sAF. However, current HbA1c and eGFR were not significantly associated to sAF (Table 3).

**Table 2. Multivariate Association* Between Diabetes and CKD During Follow-Up and sAF at 10 Years**

<table>
<thead>
<tr>
<th></th>
<th>Model, N = 328</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
</tr>
<tr>
<td>Diabetes during follow-up†</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>Recent</td>
<td>0.12</td>
</tr>
<tr>
<td>Longstanding</td>
<td>0.38</td>
</tr>
<tr>
<td>CKD during follow-up†</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>Recent</td>
<td>0.15</td>
</tr>
<tr>
<td>Longstanding</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Notes: CKD = chronic kidney disease; sAF = skin autofluorescence.  
*Estimated using a single linear regression model for diabetes and CKD, with absence of diabetes and CKD as classes of reference and adjusted for age at baseline, sex, hypertension, body mass index, hypertriglyceridemia, and smoking at baseline.  
†Recent**: participants did not have the disease at baseline and at 10-year follow-up. “Recent”; participants had the disease only at 10-year follow-up. “Longstanding”**: participants had the disease at both baseline and 10-year follow-up.

**Discussion**

AGEs have been suspected to play a role in the aging process for a long time (7), but this work is the first longitudinal study arguing for sAF of AGEs as a marker of metabolic memory in elderly participants from the general population. We found higher sAF in participants with long-standing diabetes and CKD, persisting after adjustment on age, sex, body mass index, hypertension, hypertriglyceridemia, and smoking. sAF was positively associated with 10 years earlier glycemia or HbA1c and negatively with 10 years earlier eGFR, and persisting after adjustment for other risk factors, whereas in the cross-sectional analysis, sAF was associated only with eGFR and not with current glycemia or HbA1c.

In the nondiabetic population, information on relationship between sAF and glycemia or HbA1c is scanty. Cross-sectional studies within patients with schizophrenia (15) or central obesity (16) found no association of sAF with the simultaneous glycemia, in accordance with our results. However, significantly higher sAF was repeatedly mentioned in both types of diabetes compared with healthy controls. Most of these studies highlighted an increase of sAF with increasing (self-reported) duration of type 1 diabetes (5,17–21). Type 2 diabetes is the most prevalent, as prevailing in our aged population, but its duration is not easy to appreciate because it is insidious. The relation between sAF and diabetes duration was significant in the pioneer work from Meerwaldt and colleagues (5,22), but more recent studies did not confirm this finding (21,23,24). Our study shows that sAF is higher in longstanding, than in recent diabetes.

The relation between sAF and distal—but not recent—fasting plasma glucose also argues for its value as a marker of metabolic memory. Only two studies, limited to patients with diabetes, have analyzed the cross-sectional relation between sAF and glycemia: In line with our finding, they did not find a significant association (18,25). Most of the studies that attempted to relate sAF to simultaneously determined HbA1c did not find any association, both in type 1 (17,20,21) and type 2 diabetes (5,26). This relation was detected in some reports (19): HbA1c reflects the long-term glucose control in stable patients. In the few studies where long-term HbA1c (means of HbA1c of the previous years) were registered, significant relations with sAF were reported (5,17–20). One prospective study has found a weak association between sAF and HbA1c over a short term of diabetes duration and follow-up (24): sAF poorly reflects short-term glycemic control. All these studies were performed in patients with diabetes, and this report is the first to relate sAF to plasma glucose and HbA1c 10 years before in a mixed population.

Renal function is also involved in accumulation of AGEs. To our knowledge, there was previously no information about the relation between sAF and eGFR in the general population. Few case-control
multivariate analysis shown a significant increase of sAF as the severity of CKD increases (19,21,28) and with more prolonged CKD (27).

All studies that had looked at the relation between sAF with the concomitant eGFR found a negative association (19,20,26,28,29) as we did. This contrast with the absence of relation with the simultaneous fasting plasma glucose suggests a more rapid accumulation of AGEs in CKD than in diabetes. However, these cross-sectional associations do not indicate a causal relation. As time is needed to reach irreversible forms of AGEs, this association could already reflect renal damage due to AGEs accumulation, especially in a population of elderly people (7).

Our report is the first to relate a negative association between sAF and eGFR 10 years before in general population of elderly people, also arguing for its value as a marker of metabolic memory.

Type 2 diabetes and CKD are insidious diseases; their early stages are often asymptomatic. In newly diagnosed patients, clinicians should be interested by markers of their duration to identify individuals most at risk of developing complications. By reflecting the past metabolic background, sAF could fulfill this need. Interestingly, we also found that sAF was associated to other risk factors present 10 years earlier (body mass index, hypertriglyceridemia, and smoking). It can also be noted that a high prevalence of hypertension in our population, involving high rate of angiotensin receptor blockers or angiotensin-converting enzyme use. These treatments are potentially associated with reduced AGEs formation (29) and have been taken into account in the definition of hypertension. Despite this adjustment, association between sAF and long-term glycemic and renal status persisted.

Our study has some limitations. First, sAF does not only reflect AGEs: Fluorescence of non-AGEs tissue components could be detected, whereas nonfluorescent AGEs were not measured. However, validation studies have shown a good correlation between sAF and the presence of advanced glycation endproducts (AGEs) glucosepane and methylglyoxal hydroimidazolone are independent of advanced glycation endproduct accumulation. The noninvasive method helps to distinguish diabetes older than 10 year and could therefore be of have a great clinical interest.

### Supplementary material
Supplementary material can be found at: [http://biomedgerontology.oxfordjournals.org/](http://biomedgerontology.oxfordjournals.org/)

### Acknowledgments
We thank K. Rajaobelina, A. Cougnard-Gregoire, C. Delcourt, H. Gin, P. Barberger-Gateau, and V. Rigalleau.

### Conflict of Interest
No potential conflicts of interest relevant to this article were reported.

### References


