Prediction and monitoring of chronic kidney disease

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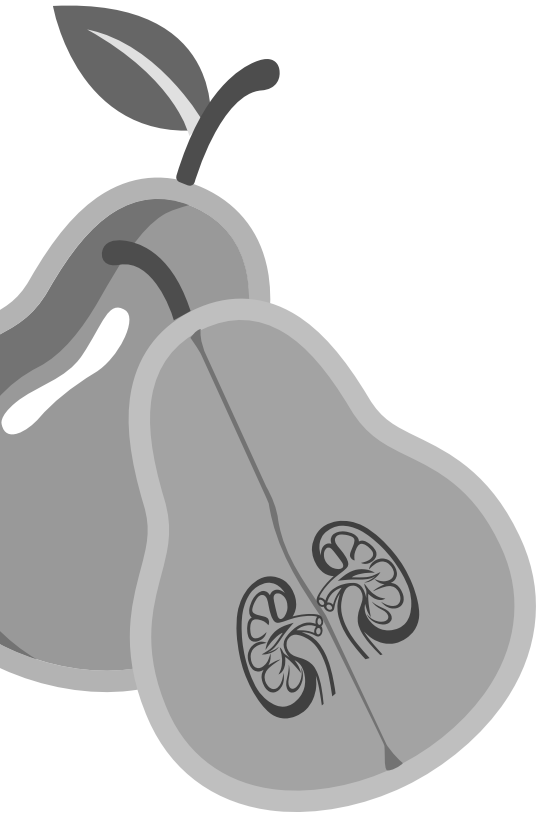
Chapter 3

The association of skin autofluorescence levels with kidney function decline in patients with peripheral artery disease



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Abstract

Objective: Skin autofluorescence (SAF), a measure of advanced glycation end product (AGE) accumulation, is associated with kidney function. We investigated the association of SAF with rate of kidney function decline in a cohort of patients with peripheral artery disease.

Approach and results: We performed a post hoc analysis of an observational longitudinal cohort study. We included 471 patients with peripheral artery disease and SAF was measured at baseline. Primary end point was rate of eGFR decline. Secondary end points were incidence of eGFR <60 and <45 ml/min/1.73m^2, as well as rapid eGFR decline, defined as a decrease in eGFR of >5 ml/min/1.73m^2 per year. During a median follow-up of 3 years, the mean change in eGFR per year was -1.8±4.4 ml/min/1.73m^2/year. No significant difference in rate of eGFR decline was observed per 1 AU increase in SAF (-0.1 ml/min/1.73m^2 per year, 95% CI -0.7 to 0.5, P=0.8). Analyses of the secondary end points showed that there was an association of SAF with incidence of eGFR <60 and <45 ml/min/1.73m^2 (HR 1.54, 95% CI 1.13-2.10 p=0.006 and HR 1.76, 95% CI 1.20-2.59, P=0.004, respectively), but after adjustment for age and gender significance was lost. There was no association of SAF with rapid eGFR decline.

Conclusions: In conclusion, in this cohort of patients with peripheral artery disease, elevated skin autofluorescence was associated with lower baseline eGFR. Although SAF has previously been established as a predictor for cardiovascular disease and mortality, it did not predict the rate of kidney function decline during follow-up in this study.

Introduction

Advanced glycation end products (AGEs) are irreversibly glycated proteins with injurious effects on tissues.[1] AGE formation is promoted by hyperglycaemic environments and oxidative stress, and has previously been associated with aging, diabetes mellitus (DM), chronic kidney disease (CKD) and cardiovascular disease.[2-13] Accumulation of AGEs on long-lived proteins such as collagen occurs in all types of tissue, including the skin, vascular tissue as well as glomerular and tubular basement membranes. Increased levels of AGEs contribute to tissue injury by activating pro-inflammatory and pro-oxidative pathways, which can cause kidney damage.[7] In turn, reduced glomerular filtration rate causes a lower rate of AGE excretion, leading to a vicious cycle of further AGE accumulation and more kidney and cardiovascular damage.[7] AGE accumulation has been and is currently being investigated as a treatment target using different approaches such as diet, improved glucose control, and specific AGE lowering drugs.[14-16]

Skin autofluorescence (SAF), measured non-invasively with an optical device, is a validated technique to assess AGE levels in the skin.[17] Peripheral artery disease (PAD) is associated with an increased risk of CKD.[18] Previously, we showed that SAF is elevated in subjects with PAD and is associated with mortality, cardiovascular events and amputation during follow-up.[10,12,13] The association of SAF and chronic kidney disease has also previously been demonstrated.[19] SAF was also found to be associated with development of albuminuria in a cohort of patients with type 2 DM.[20] SAF may therefore be a non-invasive measure to predict kidney disease progression. Since both CKD and DM increase SAF, there may be an interaction between CKD and DM in the relationship with SAF. Therefore, we investigated the associations of the presence of impaired kidney function and DM with SAF at baseline. Furthermore, we assessed, the association of baseline SAF with rate of kidney function decline during follow-up. For this study we used data of an observational cohort study that included patients with PAD. We hypothesized that increased SAF levels are independently associated with impaired kidney function and DM at baseline, and with accelerated kidney function decline during follow-up.

Methods

Materials and methods are available in the online-only Data Supplement

In short, we performed a post hoc analysis of a single-center prospective cohort study of 471 patients with established PAD. Deposition of tissue AGEs was noninvasively measured by skin autofluorescence with the AGE Reader. Five-year follow-up data were analyzed. The primary end point was rate of eGFR decline, defined as the change in eGFR in ml/min/1.73m^2 per year. For the longitudinal data analysis of the primary end point, we performed a linear mixed model analysis with the repeated measurements of eGFR as the outcome and a random effect for time, to allow for individual deviations to the overall population slope. Patients with at least two eGFR measurements were included in this analysis. All models included SAF and an interaction term between SAF and time, to allow for assessment of differences in change in eGFR over time across SAF levels (SAF*time).

Covariates that were significant in the cross-sectional multivariable analysis with SAF were included in the linear mixed model. Three models were tested: model 1; crude model including SAF, time and their interaction term; model 2, as model 1 plus age and sex; model 3, as model 2 plus smoking and diabetes. Secondary end points were incidence of eGFR <60 ml/min/1.73m^2, <45 ml/min/1.73m^2 and rapid eGFR decline, defined as an eGFR decline of >5 ml/min/1.73m^2 per year. A Cox proportional hazards regression analysis was used to assess the association of SAF with incidence of eGFR <60 ml/min/1.73m^2 and <45 ml/min/1.73m^2, and logistic regression analysis assess the association between SAF and rapid eGFR decline (coded as categorical variable).

Results

Baseline characteristics

Baseline characteristics are presented in Table 1 for the overall cohort as well as for participating subjects stratified according to SAF tertiles (<2.5, 2.5-3.1 and >3.1 AU). Mean SAF was 2.8±0.7 AU and mean age was 65.9±10.6 years, 70% were male and 31% had diabetes mellitus. Baseline eGFR was 76.9±21.5 ml/min/1.73m^2. Patients with higher SAF levels were older, more frequently had diabetes mellitus, a history of coronary artery disease and cerebrovascular disease, used beta blockers and diuretics more often, had higher HbA1c levels and lower eGFR (all P<0.05, Table 1).

Cross-sectional analysis of covariates associated with SAF

Evaluation of covariates possibly associated with SAF are shown in Table 2. Univariable and multivariable linear regression analyses showed significant associations of SAF with several covariates. In the multivariable analysis, higher levels of SAF were independently associated with being older smoking, having diabetes mellitus, and having impaired kidney function. Figure 1 shows the association of baseline diabetes status and impaired kidney function (eGFR above and below 60 ml/min/1.73m^2) with SAF, and indicates that SAF levels are dependent on presence of DM as well as impaired kidney function (P<0.001). No significant interaction was found between diabetes status and impaired kidney function versus SAF level (p for interaction 0.6), suggesting that diabetes and impaired kidney function are truly independently associated with SAF.

A sensitivity analysis replacing hypertension, hypercholesterolemia, obesity, impaired kidney function and diabetes status with baseline systolic blood pressure, total cholesterol, eGFR and HbA1c levels is shown in Supplemental Table 1. This analysis showed similar associations of SAF with age, smoking, HbA1c and eGFR. In the univariable analysis the p-value for total cholesterol met the threshold for entering the multivariable analysis (P=0.06 for total cholesterol versus P=1.0 for hypercholesterolemia in the original analysis). However, in the multivariable analysis no significant association of cholesterol with SAF was found.

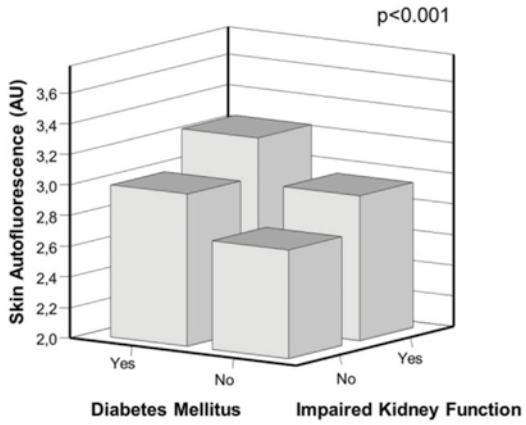

Figure 1 Bar graph showing SAF levels across groups of patients stratified according to presence or absence of diabetes and impaired kidney function (eGFR <60 ml/min/1.73m^2). P for ANOVA is given.

Longitudinal analysis of SAF and eGFR decline

During a median follow-up of 3.0 years (IQR 1.5-4.7 years), patients had on average 7.4 eGFR measurements available (range 1-81 measurements), with a median interval of 0.5 years (IQR 0.3-1.1). Twenty-eight patients without follow-up eGFR measurements were excluded from the longitudinal analysis. The overall eGFR slope for the remaining 443 patients was -1.8±4.4 ml/min/1.73m^2/year. Seventeen (4%) patients had a doubling of serum creatinine during follow-up.

The linear mixed model analysis of SAF as continuous variable with the repeated eGFR measurements as outcome showed that although patients with higher SAF levels had on average a lower eGFR at baseline (-6.5 (95% CI -9.4 to -3.6) ml/min/1.73m^2 per 1 AU increase in SAF, P<0.001), the interaction term between SAF and time was not significant (P=0.8,Table 3).

Table 1 Baseline characteristics

		SAF tertile			
	All	<2.5	2.5-3.1	>3.1	P-value
N	471	156	158	157	
Mean SAF (AU)	2.8±0.7	2.1±0.3	2.8 ±0.2	3.6 ±0.4	
Age (years)	65.9±10.6	63.0±11.4	65.6±9.9	69.0±9.7	**<0.001**
Male (%)	328 (70)	101 (65)	115 (73)	111 (71)	0.3
Smoker (%)	243 (52)	74 (48)	84 (53)	85 (54)	0.4
Fontaine class ≥3 (%)	63 (13)	16 (10)	19 (12)	28 (18)	0.2
Coronary artery disease (%)	142 (30)	35 (22)	53 (34)	54 (34)	**0.04**
Cerebrovascular disease (%)	69 (15)	14 (9)	23 (15)	32 (20)	**0.02**
BMI (kg/m^2)	26.6±4.5	26.8±4.7	26.7 ±4.4	26.4±4.5	0.8
Hypertension (%)	434 (92)	145 (93)	143 (91)	146 (93)	0.6
SBP (mmHg)	146±25	147±22	143±26	147±26	0.2
DBP (mmHg)	79±14	80±12	79±16	79±15	0.9
Antihypertensive drug use (%)	395 (84)	131 (84)	127 (80)	137 (87)	0.3
RAAS inhibitor use (%)	309 (66)	106 (68)	99 (63)	104 (66)	0.6
Alpha Blocker use (%)	24 (5.1)	7 (4.5)	7 (4.4)	10 (6.4)	0.7
Beta Blocker use (%)	232 (49)	65 (42)	78 (49)	89 (57)	**0.03**
CCB use (%)	117 (25)	35 (22)	34 (22)	48 (31)	0.1
Diuretic use (%)	149 (32)	40 (26)	48 (30)	61 (39)	**0.04**
Hypercholesterolemia (%)	405 (86)	136 (87)	131 (83)	138 (88)	0.4
Statin use (%)	354 (75)	116 (75)	113 (72)	125 (80)	0.2
Total Cholesterol (mmol/L)	4.7±1.3	4.8±1.2	4.6±1.3	4.5±1.3	0.8
Diabetes mellitus (%)	144 (31)	29 (19)	50 (32)	65 (41)	**<0.001**
Glucose lowering drug use (%)	103 (22)	15 (10	38 (24)	50 (32)	**<0.001**
Insulin (%)	43 (9)	4 (3)	12 (8)	27 (17)	**<0.001**
Oral glucose lowering drugs (%)	76 (16)	12 (8)	31 (20)	33 (21)	**0.002**
Glucose (mmol/L)	6.3±2.1	6.1±1.4	6.6±2.6	6.5±2.1	0.07
HbA1c (mmol/mol)	44.3±10.9	41.0±6.5	45.4±10.9	48.6±12.1	**<0.001**
Serum Creatinine (μ/L)	88.4±35.4	79.6±26.5	88.4±35.4	97.2±44.2	**0.009**
eGFR (ml/min/1.73m^2)	76.9±21.5	81.4±19.5	76.2±20.7	73.0±23.4	**0.002**

Table 2 Linear regression analysis of baseline SAF levels with other baseline covariates

	Univariable			Multivariable		
	Beta	95% CI	P-value	Beta	95% CI	P-value
Age	0.251	0.164 to 0.338	<0.001	0.274	0.182 to 0.367	<0.001
Male vs female	0.078	-0.550 to 0.212	0.3	-	-	-
Smoker vs non-smoker	0.113	-0.009 to 0.235	0.07	0.293	0.170 to 0.415	<0.001
Presence of:						
Hypertension	0.017	-0.211 to 0.245	0.8	-	-	-
Hypercholesterolemia	-0.002	-0.179 to 0.175	1.0	-	-	-
Diabetes mellitus	0.305	0.174 to 0.435	<0.001	0.276	0.151 to 0.401	<0.001
Impaired kidney function	0.275	0.118 to 0.431	0.001	0.177	0.023 to 0.331	0.02
Obesity	-0.026	-0.178 to 0.126	0.7	-	-	-

Beta is expressed per 1 SD increase for continuous variables and versus the reference category for dichotomous variables.

Table 3 Linear mixed models for the association of baseline SAF with change in eGFR during follow-up (ml/min/1.73m^2/year), per unit increase of SAF. The coefficient for SAF represents the association of SAF (per unit) with eGFR at baseline. The coefficient for SAF*time represents the association of baseline SAF (per unit) with eGFR slope during follow-up.

	Beta	SE	95% CI	p-value
Model 1 SAF	-6.532	1.477	-9.427 to -3.637	<0.001
SAF * time	-0.093	0.326	-0.731 to 0.545	0.8
Model 2 SAF	-2.576	1.276	-5.078 to -0.074	0.04
SAF * time	-0.119	0.326	-0.759 to 0.521	0.7
Model 3 SAF	-2.917	1.324	-5.513 to -0.322	0.03
SAF * time	-0.121	0.327	-0.762 to 0.520	0.7

Model 1: crude model including SAF, time and an interaction term for SAF*time; Model 2, as model 1 + age and sex; Model 3, as model 2 + smoking and diabetes; Random effect in all models is time (years). Beta coefficient for SAF is the overall decrease in eGFR per unit increase in SAF. The beta coefficient for the interaction term of SAF with time represents the annual change in eGFR in ml/min/1.73m^2 per unit increase in SAF.

This indicates that eGFR slopes during follow-up across SAF levels at baseline did not differ. Across SAF tertiles there was also no difference in eGFR slope: for tertile 1 (SAF <2.5 AU) -1.8±2.2, for tertile 2 (SAF 2.5 to 3.1 AU) -1.7±2.4 and for tertile 3 (SAF >3.1 AU) -2.1±2.0 ml/min/1.73m^2 per year (P=0.6 from linear mixed model analysis for both tertile 2 and 3 versus tertile 1; Figure 2).

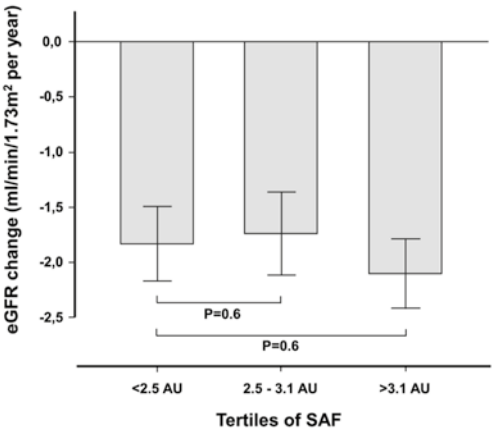

Figure 2 Mean eGFR slope during follow-up by SAF tertile at baseline with 95% confidence intervals. P-values are provided for linear mixed model analysis with the lowest tertile as reference.

The sensitivity analyses showed that patients with DM did not have a faster decline in eGFR than patients without DM (P=0.1) (Supplemental Table 2). Additionally, the interaction between SAF, DM, and time was also not significant (P=0.5), meaning that patients with DM and high levels of SAF did not have faster eGFR decline than patients without DM and lower levels of SAF. Lastly, to show the robustness of our results, we performed a linear regression analysis studying SAF levels across tertiles of eGFR change. No differences in SAF levels were found (P=0.1 for trend, Supplemental Table 3).

For the secondary outcomes (incidence of eGFR <60 and <45 ml/min/1.73m^2), 107 and 42 patients, respectively, already had eGFR below these thresholds at baseline and were excluded. During follow-up, 91 (25%) patients reached an eGFR below <60 ml/min/1.73m^2 and 59 (14%) patients reached an eGFR <45 ml/min/1.73m^2. Kaplan Meier figures for both end points are shown in Supplemental Figure 1. The figures show significant differences in event-free survival for both incident eGFR <60 ml/min/1.73m^2 (log-rank P=0.02) as well as incident eGFR <45 ml/min/1.73m^2 (log-rank P=0.002). The hazard ratios for all Cox regression models tested for both end points are listed in Supplemental Table 4. Per unit increase in SAF, patients had a 54% higher risk of developing eGFR <60 ml/min/1.73m^2 (hazard ratio [HR] 1.54, 95% CI 1.13-2.10 P=0.006) and a 76% higher risk of developing eGFR <45 ml/min/1.73m^2 (HR 1.76, 95% CI 1.20-2.59, P=0.004). However, this association lost significance for both end points after adjusting for age and sex in model 2. The associations between SAF and both end points remained not significant in model 3.

Finally, we studied the association between baseline SAF and rapid kidney function decline during follow-up. A total of 104 patients had an eGFR decline of more than 5 ml/min/1.73m^2 per year. Results of the logistic regression analysis are listed in Supplemental Table 5. The logistic regression showed no association between SAF and rapid kidney function decline in all models (P>0.05).

Discussion

Our results indicate that in patients with PAD, both diabetes mellitus and impaired kidney function were associated with increased AGE accumulation, measured as skin autofluorescence. In a multivariable analysis of the cross-sectional data, higher SAF levels were significantly associated with lower eGFR independent of age, smoking and diabetes status. However, in longitudinal analyses, we found no independent association of baseline SAF levels with eGFR decline during follow-up, incidence of eGFR <60 ml/min/1.73m^2 or eGFR <45 ml/min/1.73m^2, or rapid eGFR decline. Furthermore, we found no interaction between SAF and DM on eGFR decline.

The finding that SAF is cross-sectionally associated with impaired kidney function confirms the findings of earlier studies.[20,21] However, the longitudinal analyses in our cohort, showed no association between SAF and eGFR decline. Only one study has previously investigated the relationship between SAF and kidney function outcome. That study showed, in a cohort of 449 Japanese pre-dialysis CKD patients with a 32% diabetes prevalence, that SAF predicted the rate of kidney function decline and incidence of end-stage kidney disease.[11] The discrepant findings in our study versus those in the study by Tanaka et al may be due to population differences between the cohorts. For Caucasians, the reference value of SAF in healthy individuals is 2.46±0.57 for the age group of 60 to 70 years, and SAF has been shown to increase with approximately 0.023 AU per year.[22] Our cohort had a mean SAF of 2.8 AU versus 2.1 AU in the other cohort, suggesting that our cohort was in poorer health. In addition, the other study included only Japanese patients, whereas we included Dutch patients. Others have shown in a large cohort of CKD patients from 3 different ethnic origins (Caucasian, Oriental Asian and South Asian), that both Asian groups had faster progression towards end-stage kidney disease than the Caucasian group.[23] In addition, the subjects from the Tanaka cohort were selected to have CKD. In line, average baseline eGFR was 55.8 ml/min/1.73m^2, whereas in our study it was 76.9 ml/min/1.73m^2 although age was similar in the two cohorts (64.0 and 65.9 years, respectively). Subjects with lower eGFR are known to have a higher risk for adverse kidney outcomes during follow-up.[24] Indeed in the Tanaka study 11% reached end-stage renal disease or doubling of serum creatinine during follow-up, and this figure was considerably lower in our cohort. The more rapid rate of eGFR decline in the Asian cohort may have increased the sensitivity for finding significant associations between SAF and kidney end points. Furthermore, it is known that AGEs accumulate in case of impaired kidney function, creating a vicious cycle of AGE accumulation, leading to further kidney damage with even more reduced excretion of AGEs, and further AGE accumulation.[7] Given the difference in baseline eGFR between our cohort and the Japanese cohort and our discrepant findings, it is possible that this vicious cycle only occurs in established CKD with eGFR levels below a certain threshold.

Our cohort had a high prevalence of (severe) cardiovascular co-morbidity, which is independently associated with SAF,[10,25] but most patients had preserved kidney function. Furthermore, others have shown that SAF serves as a marker of metabolic memory, reflecting glycemic and renal status over the previous 10 years.[26] We found a significant cross-sectional association of SAF with eGFR, but did not find an association of SAF with eGFR decline. Additionally, there was no interaction between SAF and DM on eGFR decline. It is therefore possible that SAF is merely a marker of impaired kidney function and metabolic memory, and not a risk factor for further kidney function decline.

A limitation of our study is that SAF was measured only at baseline. Furthermore, data on albuminuria was not available. However, it may be expected that additional adjustment for albuminuria could only have weakened the association between SAF and kidney function decline in our analyses. Lastly, creatinine was only measured on indication by regular medical caregivers of the patients included in our cohort. This may have resulted in bias, with relatively more information on eGFR during follow-up being available in patients at highest risk for kidney function decline. However, since this bias would lead to a higher chance of finding a significant association of SAF with kidney function decline, this only strengthens our negative findings. Strengths of this study were that we investigated a relatively large cohort, and that longitudinal associations of SAF with eGFR slopes have not been investigated before in a Caucasian cohort.

Given the presently available findings the future of SAF as a potential risk factor for adverse renal outcome and as screening tool to identify subjects at risk for accelerated kidney function decline remains unclear. We found no association of SAF with eGFR decline in patients with PAD, which conflicts with earlier findings that showed a significant association of SAF with eGFR decline in patients with established CKD.[11] Therefore the use of SAF as a predictor of kidney function decline may be limited to patients without cardiovascular comorbidity, or SAF may only be a predictor in patients with established CKD. Further research is needed to clarify if, and in which populations SAF can predict kidney function decline. Such studies should preferably include mixed populations to allow within study subgroup analyses. In addition, to our knowledge it has not been investigated whether serial measurements of SAF may further improve the calculation of cardiovascular and/or kidney risk. It may be that changes in SAF are more strongly associated with eGFR decline than a single SAF measurement.

In conclusion, in this cohort of patients with peripheral artery disease, elevated skin autofluorescence was associated with lower eGFR levels at baseline. Although skin autofluorescence has previously been established as a predictor for cardiovascular disease and mortality, it did not predict the rate of kidney function decline during follow-up.

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Supplemental Tables and Figures

Supplemental Table 1 Linear regression analysis of baseline SAF levels with covariates

	Univariable			Multivariable		
	Beta	95% CI	P	Beta	95% CI	P
Age	0.251	0.164 to 0.338	**<0.001**	0.192	0.074 to 0.310	**0.001**
Male vs female	0.078	-0.550 to 0.212	0.3	-	-	-
Smoker vs non-smoker	0.113	-0.009 to 0.235	0.07	0.394	0.192 to 0.596	**<0.001**
SBP	-0.014	-0.105 to 0.077	0.8	-	-	-
Total Cholesterol	-0.094	-0.189 to 0.003	0.06	-0.052	-0.149 to 0.045	0.3
HbA1c	0.264	0.167 to 0.360	**<0.001**	0.190	0.092 to 0.287	**<0.001**
eGFR	-0.206	-0.295 to -0.117	**<0.001**	-0.115	-0.227 to -0.002	**0.05**
BMI	-0.020	-0.112 to 0.071	0.7	-	-	-

Beta is expressed per 1 SD increase for continuous variables and versus the reference category for dichotomous variables.

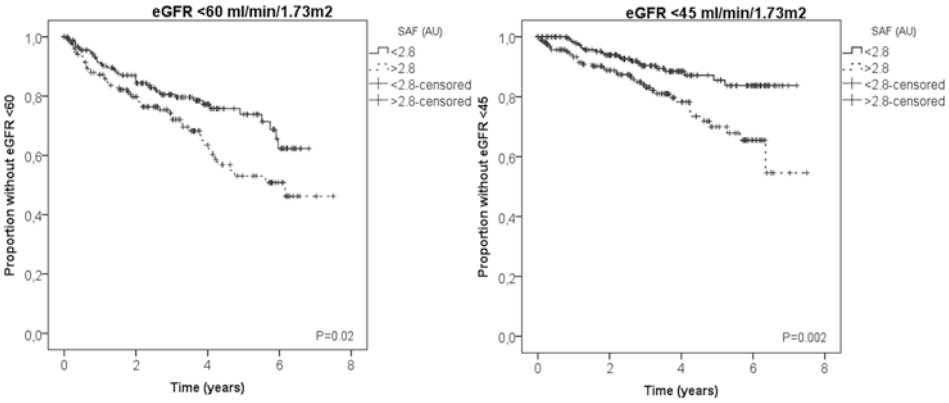
Supplemental Table 2 Linear mixed models for the association of DM with change in eGFR during follow-up (ml/min/1.73m^2/year), and a model including the interactions between SAF and time, DM and time, and the three-way interaction between SAF, DM and time, to assess whether the association of SAF with eGFR decline is stronger in patients with diabetes compared to patients without diabetes.

	Beta	SE	95% CI	P-value
Model 1 SAF	-6.122	1.513	-9.089 to -3.156	<0.001
SAF*Time	-0.004	0.329	-0.649 to 0.641	1.0
DM	-1.801	2.206	-6.129 to 2.528	0.4
DM*Time	-0.709	0.462	-1.614 to 0.197	0.1
Model 2 SAF	-6.120	1.513	-9.086 to -3.154	<0.001
DM	-1.807	2.209	-6.135 to 2.522	0.4
SAF*Time	-0.152	0.402	-0.940 to 0.635	0.7
DM*Time	-1.973	2.018	-5.928 to 1.981	0.3
DM*SAF*Time:	0.438	0.680	-0.896 to 1.772	0.5

Model 1: crude model including SAF, DM, time, and interaction terms for SAF*Time and DM*time; Model 2; model including SAF, DM, time, and an interaction term between SAF*Time and DM*time, plus a three-way interaction term between DM, SAF, and time. Random effect in all models is time (years). Beta coefficient for SAF is the overall decrease in eGFR per unit increase in SAF. Beta coefficients for interaction terms between SAF and time represent the change in eGFR in ml/min/1.73m^2/year per unit increase of SAF. Beta coefficient for the interaction terms of DM and time represent the change in eGFR in ml/min/1.73m^2/year for patients with DM versus patients without DM. The beta coefficient for the interaction term of DM, SAF, and time represents the change in eGFR in ml/min/1.73m^2/year, per unit increase of SAF for patients with DM.

Supplemental Table 3 Mean SAF levels (AU) for tertiles of eGFR change per year (ml/min/1.73m^2/year)

	eGFR slope (ml/min/1.73m^2/year			
	<-3.4	-3.3-0.0	>0.1	P for trend
SAF (AU)	2.9±0.6	2.7±0.7	2.9±0.7	0.1



Supplemental Figure 1 Kaplan Meier curves showing per SAF category (below and above median of the total group) the proportion of participants without eGFR <60 ml min^{-1} 1.73m$^{2\ -1}$ (left panel) eGFR <45 ml min^{-1} 1.73m$^{2\ -1}$ (right panel), and p-values for the log-rank test.

Supplemental Table 4 Cox regression analysis of baseline SAF and endpoints at follow-up, hazard ratio + 95% confidence interval

	HR	95% CI	P-value
eGFR <60			
Model 1	1.54	1.13-2.10	0.006
Model 2	1.18	0.85-1.65	0.3
Model 3	1.15	0.97-1.67	0.5
eGFR <45			
Model 1	1.76	1.20-2.59	0.004
Model 2	1.43	0.96-2.13	0.08
Model 3	1.31	0.87-1.97	0.2

Model 1: crude model ; Model 2, as model 1 + age and sex; Model 3, as model 2 + smoking and diabetes

Supplemental Table 5 Logistic regression analysis of baseline SAF with rapid eGFR decline (>5 ml min^{-1} 1.73$m^{2\,-1}$ decline per year), odds ratio + 95% confidence interval

	OR	95% CI	P-value
Model 1	1.36	0.99-1.88	0.06
Model 2	1.34	0.97-1.88	0.08
Model 3	1.10	0.75-1.59	0.6

Model 1: crude model ; Model 2, as model 1 + age and sex; Model 3, as model 2 + smoking and diabetes