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Factors Associated With Change in Skin Autofluorescence, a Measure of Advanced Glycation End Products, in Persons Receiving Dialysis

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Introduction: An increase over time in skin autofluorescence (SAF), a measure of accumulation of advanced glycation end products (AGE), predicts higher mortality on hemodialysis (HD). However, evidence is lacking regarding factors that contribute to changes in SAF over time in populations on dialysis. We investigated the rate of change in SAF over 1 year and the factors associated with these changes.

Methods: We enrolled 109 patients on HD and 28 on peritoneal dialysis in a prospective study. SAF was measured at baseline, 3, 6, 9, and 12 months. Rate of change in SAF was calculated using the SLOPE function in Microsoft Excel (Microsoft, Redmond, WA). Participants were then grouped into those with stable SAF or increasing SAF. Dietary AGE intake and nutritional assessments were performed at baseline, 6, and 12 months.

Results: The mean SAF trend observed was an increase of 0.30 $\pm$ 0.63 arbitrary units (AU) per year, but this varied from a decrease of 0.15 $\pm$ 0.44 to an increase of 0.76 $\pm$ 0.42 AU per year in stable and increasing SAF groups, respectively. Increasing SAF was more common in participants who developed malnutrition during the observation period, whereas those who became well-nourished were more likely to have stable SAF (8 [80%] vs. 14 [42%]; $P = 0.02$). Development/prevalence of malnutrition over 1 year, HD as first dialysis modality, and current smoking were independent predictors of increasing SAF.

Conclusion: SAF increases over time in most persons on dialysis. Independent determinants of increasing SAF were development/prevalence of malnutrition, HD as first dialysis modality, and current smoking. Strategies to reduce/prevent the rise in SAF, including prevention/correction of malnutrition, should be investigated in prospective studies.

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Advanced glycation end products (AGEs) are a heterogeneous group of molecules that result from the nonenzymatic glycation of proteins, lipids, and nucleic acids.[1] Moreover, AGEs are uremic toxins that are markedly increased in persons with chronic kidney disease (CKD), particularly on dialysis, owing to increased production, impaired excretion, and inefficient removal.[2,3] AGEs are rapidly formed either endogenously during hyperglycemia and oxidative stress or through exogenous sources such as cigarette smoke and food.[1] AGEs form crosslinks between tissue protein molecules and interact with specific AGE receptors, resulting in systemic inflammation and, consequently, exacerbation of tissue damage.[4]

Tissue AGE accumulation can be assessed noninvasively, using SAF. Several cross-sectional studies have reported that persons on dialysis have increased SAF and that factors such as chronological age, diabetes, dialysis vintage, and glucose exposure from peritoneal dialysis (PD) fluid are associated with higher SAF in this population.[5,6] We have also shown that smoking and markers of malnutrition, such as serum albumin, handgrip strength (HGS), and protein intake, are independent determinants of increased SAF in patients on HD.[7]

Previous observational studies have shown that higher baseline SAF is strongly associated with

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increased mortality in the dialysis population.[8–11] In addition, Arsov *et al*.[12] reported that an increase in SAF over time predicts higher mortality on HD; however, factors that contribute to the increase in SAF over time in the dialysis population have not been adequately investigated. One prospective study has reported that dialysis vintage, lower dietary AGE intake, and lower calorie intake were associated with 1-year increase in SAF in univariable analysis in a HD population, but that a body mass index (BMI) lower than or higher than 24 kg/m^2 was the sole independent predictor for this observed change.[13] Another 1-year observational study in patients on HD found that older age and use of insulin, lanthanum carbonate, and warfarin were independent predictors of the 1-year increase in SAF in multivariable analysis, whereas a vegetarian diet and residual urine output >250 ml/d were independently associated with a stable SAF.[14] It would seem, therefore, that further investigations regarding factors that contribute to changes in SAF over time in the dialysis population are needed. Thus, we aimed to investigate the rate of change in SAF over 1 year, and the factors associated with these changes, with a particular focus on nutritional aspects.

METHODS

Study Population

This was a single-center, prospective observational study conducted in the Department of Renal Medicine, Royal Derby Hospital. Persons receiving HD and performing PD who were ≥18 years of age and were able to give written informed consent were eligible. We enrolled 109 current HD and 28 current PD patients from September 2016 to August 2017, and followed them up for 1 year. Participants on HD were dialyzed at least 3 times per week, for 3 to 4 hours, with high-flux polysulphone, polyarylethersulfone, or polyvinylpyrrolidone dialyzers, whereas PD participants dialyzed using lactate/bicarbonate-buffered 1.36% and 3.86% glucose (Physioneal, Baxter Healthcare Corporation, Deerfield, IL), 7.5% icodextrin (Extraneal, Baxter Healthcare Corporation), and/or 1.1% aminoacid-containing solutions (Nutrineal, Baxter Healthcare Corporation). The following exclusion criteria were used: pregnancy or intending pregnancy, breastfeeding, and having dark skin color. Written informed consent was obtained from all participants, and ethical approval was granted by the local Research Ethics Committee (East Midlands, Nottingham 1. REC reference: 16/EM/0243).

Data Collection

Baseline participant characteristics—including chronological age, sex, ethnicity, dialysis vintage (i.e., time since first dialysis treatment), dialysis adequacy (Kt/V weekly in PD and per session in HD), blood results, current comorbidities, and history of cardiovascular disease—were extracted from electronic medical records. Information regarding educational level, occupation, and smoking status was obtained from direct interview. Diabetes was defined by clinical diagnosis. The volume of 1.36% and 3.86% glucose-containing PD solutions used per week at the time of recruitment was obtained, and the magnitude of total peritoneal glucose exposure was then estimated by multiplying the dialysis vintage by the weekly glucose load as previously described.[5]

Skin Autofluorescence Measurement

SAF was measured using a validated Autofluorescence Reader (AGE Reader, DiagnOptics, Groningen, The Netherlands). The method has been previously described in more detail elsewhere.[8] In brief, the AGE reader illuminates a skin surface of approximately 1 cm^2, protected from surrounding light, with an excitation light source between 300 and 420 nm. The emission light from the skin is measured with a spectrometer (AVS-USB2000, Avantes Inc., Eerbeek, The Netherlands) in the 300- to 600-nm range, using a 200-μm glass fiber. SAF is then calculated as the ratio between emission and excitation by dividing the average emitted light intensity between 420 and 600 nm by the amount of excitation light between 300 and 420 nm, and is expressed as AU. SAF measurements were conducted on the volar side of the forearm at approximately 10 cm below the elbow, ensuring that the area had normal skin without visible vessels, tattoos, scars, or other abnormalities. Three SAF readings were conducted on the nonfistula arm or the dominant arm if this did not have a fistula, and within the first hour of HD treatment. The mean value of 3 SAF readings was used for statistical analyses. SAF measurements may be affected by skin color and pigmentation. The AGE reader has been validated in persons with skin reflectivity >6% (i.e., Fitzpatrick skin color type I–IV).[15] Persons with darker skin color (i.e., Fitzpatrick skin color type V–VI and ultraviolet reflectance <6%) absorb high amounts of the excited light. Consequently, SAF might not be reliable in this population, and persons with dark skin were therefore excluded. When the skin reflectivity is <6%, the AGE reader gives a warning that the reflectance signal is too low to obtain valid results. It has been previously reported that SAF readings have good reproducibility and repeatability (i.e., coefficient of variation of 7%–8%).[16]

SAF was measured at baseline, 3, 6, 9, and 12 months. The rate of change of SAF among these 5 time points (i.e., SAF trend) was then calculated by fitting a regression line using the SLOPE function in Microsoft

Excel 2013, where the y-axis represented SAF values and the x-axis represented time points.[17] Participants were then grouped into those with stable SAF (slope of SAF below the median) or increasing SAF (slope of SAF above the median).

Nutritional Assessments

Detailed nutritional assessments were undertaken at baseline, 6, and 12 months and included the following:

Dietary Intake

Information regarding energy, protein and fat intake was obtained from 3 24-hour dietary recalls. Participants were asked to recall all foods and drinks they had the day before. Dietary recalls were analysed with the software Dietplan 7 (Forestfield Software Limited, West Sussex, UK) to calculate the average energy, protein, and fat intake. Average daily intake of energy and protein was then calculated in kilocalories and grams, respectively, and expressed per kilogram of ideal body weight. Dietary AGE intake (reported in kilounits/d) was estimated with a food frequency questionnaire previously validated in persons with diabetes.[18]

Anthropometry

Postdialysis weight, height, mid-arm circumference (MAC), and triceps skinfold thickness (TSF) were measured according to international standards for anthropometric assessment.[19] BMI was reported in kg/m^2, and mid-arm muscle circumference (MAMC) was calculated using the following equation: MAMC (cm^2) = MAC − (3.14 × TSF), whereas MAC and TSF were measured in cm.

Handgrip Strength

Handgrip strength (HGS) measurement was conducted within the first hour of HD treatment or during PD clinic visits using the Takei 5401 handgrip digital dynamometer (Takei Scientific Instruments Co., Ltd., Tokyo, Japan). HGS was measured in the nonfistula arm or the dominant arm if the participant did not have a fistula as described elsewhere.[7]

Subjective Global Assessment

The 7-point scale subjective global assessment (SGA) was performed to evaluate the nutritional status.[20] Based on the ratings of 6 individual core components (i.e., history of weight loss; dietary intake; gastrointestinal symptoms; functional capacity; presence of comorbidities; and subjective physical examination of subcutaneous fat mass loss, muscle wasting, and presence of oedema), nutritional status can be classified into normal nutritional status (scores of 6 or 7), mild-to-moderate malnutrition (scores of 3–5) or severe malnutrition (scores of 1 or 2). For statistical analysis, participants were placed in 2 groups: well-nourished (SGA scores 6–7) or malnourished (SGA scores 1–5).

Statistical Analyses

Data management and statistical analyses were performed using the statistical software SPSS version 24.0 (IBM Corporation, Chicago, IL). Data are presented as mean ± SD, median (interquartile range [IQR]), percentages or odds ratio (95% confidence intervals [CIs]), as appropriate. Missing data were omitted (C-reactive protein [CRP] and HGS, $n = 5$). For intragroup comparisons, Wilcoxon test was used in the case of continuous variables. Intergroup comparisons, including the subgroup comparison analysis of change in SAF by nutritional status, were performed using Mann-Whitney U test for continuous variables and χ^2 test or Fisher's exact test for categorical variables. Multivariable logistic regression analysis was performed to identify the determinants associated with change in SAF over 1 year. We selected the variables on the basis of a P value < 0.1 on univariable analysis (HD as first modality) or biological plausibility (chronological age, sex, diabetes, smoking status, new or prevalent malnutrition, and CRP). Because the distribution of CRP was highly skewed, this variable was natural log-transformed for the logistic regression analysis. Nagelkerke R^2 for the model and Hosmer and Lemeshow test P value were reported. For all statistical analyses, a P value <0.05 was considered to have statistical significance.

RESULTS

Study Population Characteristics

Baseline participant characteristics are shown in Table 1. Mean age of the whole cohort was 65 ± 14 years. Ninety (66%) participants were male, 124 (91%) were white, and 77 (56%) commenced dialysis on HD. Current smoking and malnutrition were present in 20 (15%) and 49 (36%) participants, respectively. Participants evidenced high mean dietary AGE intake (14,768 ± 7659 kU/d), whereas energy and protein intake were found to be low in comparison with estimated nutritional requirements.[21,22] During follow-up, 11 participants died, 7 were transplanted, 1 withdrew consent, and 1 recovered kidney function. Four PD patients switched to HD, and 1 HD patient switched to PD.

Factors Associated With Change in Skin Autofluorescence

Study population characteristics by slope of change in SAF are shown in Table 1. The mean SAF trend observed was an increase of 0.3 ± 0.6 AU/yr. Mean SAF trends in the stable and increasing SAF groups were −0.15 ± 0.44 AU/yr and 0.76 ± 0.42 AU/yr, respectively. Participants who evidenced an increase in SAF over 12 months were more likely to have had HD as their first modality than those who had stable SAF

Table 1. Baseline characteristics including clinical, biochemical and nutritional data by slope of change in SAF below (stable SAF) or above (increasing SAF) the median

Variable	Overall (n = 137)	Stable SAF (n = 69)	Increasing SAF (n = 68)	P value
Skin autofluorescence slope (AU)	0.30 ± 0.63	−0.15 ± 0.44	0.76 ± 0.42	<0.0001
Age, yr	65 ± 14	64 ± 13	65 ± 15	0.4
Male, *n* (%)	90 (66)	47 (68)	43 (63)	0.5
White ethnicity, *n* (%)	124 (91)	60 (87)	64 (94)	0.5
HD at baseline, *n* (%)	109 (80)	52 (75)	57 (84)	0.2
HD as first modality, *n* (%)	77 (56)	29 (42)	48 (71)	0.001
Educational qualifications, *n* (%)	79 (58)	40 (58)	39 (57)	0.9
Unemployed, *n* (%)	104 (76)	48 (70)	56 (82)	0.08
Current smoking, *n* (%)	20 (15)	7 (10)	13 (19)	0.1
Diabetes, *n* (%)	57 (42)	32 (46)	25 (37)	0.2
Malnutrition, *n* (%)	49 (36)	29 (42)	20 (29)	0.1
Coronary heart disease, *n* (%)	54 (39)	29 (42)	25 (37)	0.5
Peripheral vascular disease, *n* (%)	9 (7)	8 (12)	1 (2)	0.02
Duration nephrology care, mo	80 (43–146)	65 (45.5–134)	96 (40.5–154)	0.4
Dialysis vintage, mo	27 (10–68)	31 (13.5–68.5)	22 (6.0–65)	0.2
Dialysis adequacy (Kt/V)	1.47 ± 0.59	1.51 ± 0.62	1.41 ± 0.57	0.2
Hemoglobin (g/l)	117 ± 13	117 ± 13	117 ± 13	0.8
Serum albumin (g/l)	31.6 ± 4.3	31.7 ± 4.4	31.6 ± 4.3	0.9
C-reactive protein (mg/l)	8.0 (4.0–17.0)	8.0 (4.0–17.0)	7.0 (3.0–17.0)	0.6
Total cholesterol (mmol/l)	4.1 ± 1.2	4.1 ± 1.1	4.1 ± 1.3	0.4
Urea (mmol/l)	17.5 ± 5.2	17.6 ± 5.6	17.4 ± 4.9	0.6
Serum creatinine (μmol/l)	642 ± 207	653 ± 216	630 ± 198	0.9
Serum phosphate (mmol/l)	1.57 ± 0.51	1.58 ± 0.51	1.55 ± 0.51	0.8
Serum corrected calcium (mmol/l)	2.43 ± 0.13	2.44 ± 0.14	2.43 ± 0.13	0.4
Serum potassium (mmol/l)	4.6 ± 0.7	4.6 ± 0.8	4.6 ± 0.7	0.08
Dietary AGE intake (kU/d)	14,768 ± 7659	15,729 ± 8371	13,792 ± 7454	0.2
Energy intake (kcal/kg per d)	21.1 ± 7.6	21.3 ± 8.2	21.0 ± 7.0	0.6
Protein intake (g/kg per d)	0.89 ± 0.28	0.88 ± 0.29	0.90 ± 0.27	0.6
Fat intake (g/d)	59.1 ± 30.0	57.5 ± 30.6	60.7 ± 29.6	0.9
Dry weight (kg)	79.3 ± 20.2	77.0 ± 16.8	81.6 ± 23.1	0.06
Body mass index (kg/m^2)	27.7 ± 6.2	27.1 ± 5.3	28.3 ± 7.0	0.08
Handgrip strength (kg)	23.0 ± 11.0	23.3 ± 11.3	22.7 ± 10.8	0.8
Mid-arm muscle circumference (cm^2)	25.6 ± 3.7	25.3 ± 3.5	25.9 ± 3.9	0.7
Triceps skinfold thickness (mm)	17.2 ± 7.3	16.7 ± 6.6	17.7 ± 8.0	0.04

AGE, advanced glycation end products; AU, arbitrary units; kU, kilounits; HD, hemodialysis; SAF, skin autofluorescence.
Values expressed as mean ± SD, except for duration of nephrology care, dialysis vintage, and C reactive protein which were expressed as median (IQR).
Groups for comparison were defined according to SAF slope values below *Stable SAF* or above *Increasing SAF* the median.
P value is for comparison of data for the *Stable SAF* vs. *Increasing SAF* groups.

(48 [71%] vs. 29 [42%]; $P = 0.001$). Triceps skinfold thickness was significantly lower in the stable SAF group compared with the increasing SAF group. No associations were observed with multiple other risk factors. Analysis of the impact of total peritoneal glucose exposure on SAF found no statistically significant difference between the median values in the stable SAF and increasing SAF groups (13,209 g [3237–38,318 g] vs. 12,757 g [4474–44,554 g]; $P = 0.7$).

Changes in dietary intake and SGA score over 1 year in stable SAF and increasing SAF groups are shown in Table 2. At 6 months, mean SGA score improved significantly in the stable SAF group compared with baseline (5.8 ± 1.5 vs. 6.3 ± 1.5; $P = 0.006$), but no significant change was observed in the increasing SAF group (5.9 ± 1.6 vs. 6.2 ± 1.6; $P = 0.08$). A significant increase in mean dietary AGE intake from baseline to 12 months was observed in the increasing SAF group (14,195 ± 8012 vs.16,593 ± 10,904; $P = 0.01$) but not in the stable SAF group. Energy, protein, and fat intake remained unchanged over 1 year in both groups.

Change in Skin Autofluorescence by Nutritional Status

A subgroup comparison analysis between stable SAF versus increasing SAF by nutritional status was conducted in 117 participants who completed 12 months of follow-up (Figure 1). These participants were classified according to their nutritional status over 1 year into the following groups: well-nourished throughout 1 year ($n = 66$), malnourished throughout 1 year ($n = 17$), well-nourished at baseline but malnourished at either 6

Table 2. Change in dietary intake and Subjective Global Assessment score by stable SAF and increasing SAF

Variable	Baseline		Month 6		Month 12	
	Stable SAF (n = 59)	Increasing SAF (n = 58)	Stable SAF (n = 59)	Increasing SAF (n = 58)	Stable SAF (n = 59)	Increasing SAF (n = 58)
Dietary AGE intake (kU/d)	15,310 ± 8265	14,195 ± 8012	16,522 ± 8475	14,941 ± 7759	15,760 ± 9030	16,593 ± 10,904[a]
Energy intake (kcal/kg per d)	20.4 ± 8.1	21.6 ± 7.1	20.9 ± 7.6	22.1 ± 6.9	22.3 ± 8.9	22.8 ± 10.5
Protein intake (g/kg per d)	0.84 ± 0.27	0.91 ± 0.28	0.86 ± 0.28	0.87 ± 0.27	0.88 ± 0.31	0.88 ± 0.39
Fat intake (g/d)	55.2 ± 30.6	63.2 ± 30.2	57.3 ± 27.9	61.2 ± 22.6	59.9 ± 32.3	64.9 ± 40.4
SGA score	5.8 ± 1.5	5.9 ± 1.6	6.3 ± 1.5[b]	6.2 ± 1.6	6.0 ± 1.6	5.9 ± 2.0

AGE, advanced glycation end products; kU, kilounits; SAF, skin autofluorescence, SGA, Subjective Global Assessment.
[a]$P = 0.01$ compared with baseline.
[b]$P = 0.006$ compared with baseline.
Values expressed as mean ± SD.

or 12 months ($n = 10$), and malnourished at baseline but well-nourished at either 6 or 12 months ($n = 24$). Participants who remained well-nourished throughout 12 months evidenced equal proportions with stable or increasing SAF, whereas those who remained malnourished and those who became well-nourished evidenced a greater proportion with stable SAF than increasing SAF. In contrast, 80% of participants who were well-nourished initially but developed malnutrition, either at 6 or 12 months, evidenced increasing SAF.

Determinants of Change in Skin Autofluorescence

Multivariable logistic regression analysis with increasing SAF versus stable SAF as the dependent variable identified HD as first dialysis modality, current smoking, and the prevalence or development of malnutrition over 1 year as independent predictors of increasing SAF, but chronological age, sex, diabetes, and baseline CRP were not (Table 3).

DISCUSSION

In this prospective study, we found that SAF increases over time in most persons receiving dialysis. We also identified that prevalence or development of malnutrition over 1 year, current smoking, and HD as first dialysis modality were independent predictors of increasing SAF. Of note, dietary AGE intake was not an independent determinant of the 1-year increase in SAF

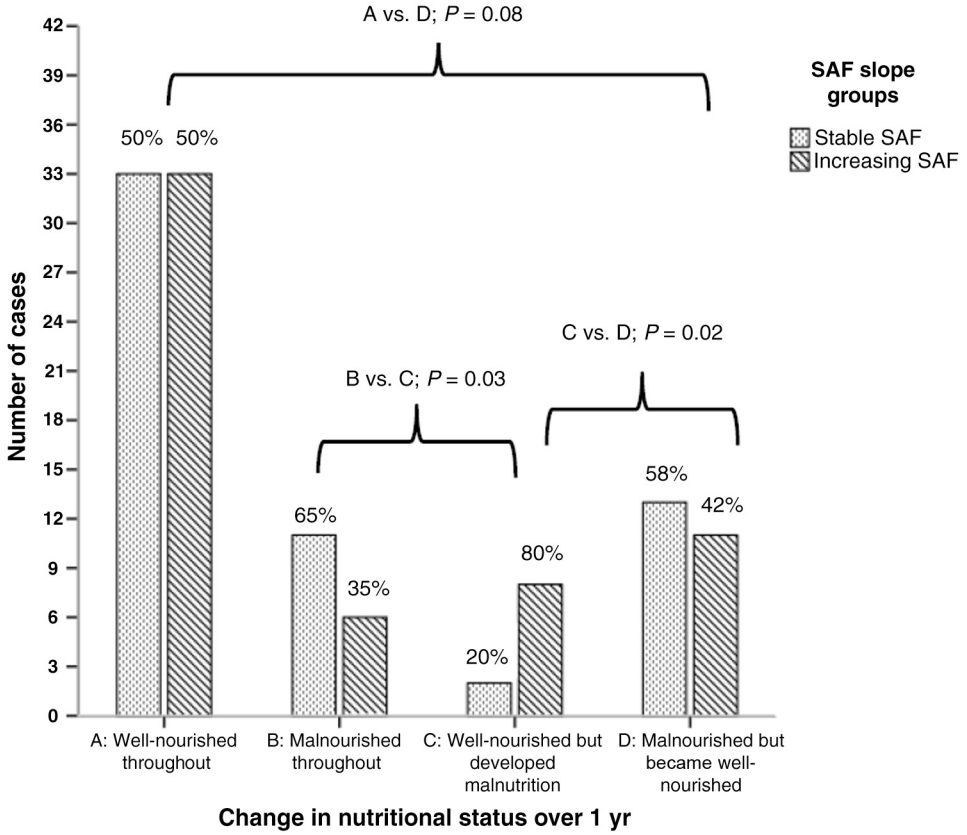

Figure 1. Prevalence of stable versus increasing skin autofluorescence levels over 1 year by change in nutritional status over 1 year. SAF, skin autofluorescence.

Table 3. Logistic regression analysis showing predictors of the pattern of change in skin autofluorescence over 12 months: increasing SAF versus stable SAF

	Univariable analysis		Multivariable analysis	
Predictor	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age (yr)	1.01 (0.98–1.03)	0.6	1.00 (0.97–1.03)	1.0
Female	1.29 (0.60–2.76)	0.5	1.61 (0.65–4.02)	0.3
No educational qualifications	1.03 (0.49–2.15)	0.9		
Current smoking	1.74 (0.62–4.85)	0.3	4.44 (1.09–18.02)	0.04
HD as first dialysis modality	3.24 (1.51–6.94)	0.002	3.75 (1.60–8.80)	0.002
Diabetes	1.58 (0.76–3.30)	0.2	1.77 (0.77–4.10)	0.2
Prevalence/development of malnutrition	1.65 (0.77–3.56)	0.2	3.74 (1.29–10.83)	0.02
Dialysis vintage (mo)	1.00 (0.99–1.01)	0.9		
Serum albumin (g/l)	1.02 (0.93–1.11)	0.7		
Log C reactive protein (mg/l)	0.90 (0.42–1.90)	0.8	1.13 (0.50–2.58)	0.8
Total cholesterol (mmol/l)	0.95 (0.69–1.30)	0.8		
Urea (mmol/l)	0.99 (0.93–1.06)	0.9		
Dietary AGE intake (kU/d)	1.00 (1.00–1.00)	0.4		
Energy intake (kcal/kg per d)	1.01 (0.96–1.06)	0.8		
Protein intake (g/kg per d)	1.89 (0.50–7.16)	0.4		
Fat intake (g/d)	1.01 (0.99–1.02)	0.3		
Dry weight (kg)	1.01 (0.99–1.02)	0.5		
Body mass index (kg/m^2)	1.01 (0.96–1.07)	0.6		
Handgrip strength (kg)	1.00 (0.96–1.03)	0.9		
Mid-arm muscle circumference (cm^2)	1.01 (0.92–1.11)	0.8		
Triceps skinfold thickness (mm)	1.01 (0.97–1.06)	0.6		

AGE, advanced glycation end products; CI, confidence interval; kU, kilounits; HD, hemodialysis; OR, odds ratio.
Nagelkerke R^2 for the model was 0.208. Hosmer and Lemeshow test *P* value was 0.599.

in this dialysis population. These observations confirm the findings of a previous cross-sectional study, which reported that several markers of malnutrition were more important determinants of higher SAF than dietary intake of AGEs in persons receiving HD.[7]

The mean SAF trend observed in our dialysis population was an increase of 0.3 ± 0.6 AU/yr. Some researchers have found a lower 1-year increase in SAF (0.15 ± 0.09 AU[13] and 0.16 ± 0.06 AU[12]), whereas others have reported an increase of 0.48 ± 0.16 AU.[14] However, these studies measured SAF only twice, at 12 months apart, and are therefore subject to the statistical phenomenon known as *regression to the mean* (i.e., those participants with high values at baseline would likely have lower values on remeasurement, and *vice versa*), whereas we have used multiple SAF measurements to derive a more robust trend over time.

In this study, the majority of the participants who developed malnutrition over 1 year evidenced increasing SAF, whereas those who became well-nourished were more likely to have stable SAF. Moreover, prevalence or development of malnutrition over 1 year was an independent determinant of increasing in SAF in multivariable analysis. These results confirm the previous observations of a cross-sectional study conducted in a HD population in which presence of malnutrition, lower serum albumin, and lower urea were significantly associated with higher SAF levels in univariable analysis, and lower protein intake, lower HGS, and lower serum albumin (all markers of malnutrition) were independent predictors of higher SAF.[7] We propose that the association between malnutrition and higher SAF might be explained in part by a vicious cycle that develops among systemic inflammation, oxidative stress, and malnutrition observed in the dialysis population. Systemic inflammation causes oxidative stress and *vice versa*; oxidative and inflammatory processes have synergistic effects on increasing protein catabolism and muscle mass loss and decreasing appetite, as well as hepatic albumin synthesis, which ultimately lead to the development of malnutrition.[23,24] Thus, factors that contribute to the development of malnutrition are likely to increase formation of AGE, and malnutrition, in turn, exacerbates these factors.

We have also observed in this study that current smoking was a significant and independent predictor of increasing SAF, confirming observations in previous cross-sectional studies conducted in healthy patients, patients with diabetes, and patients on HD that have reported that smoking is independently associated with higher SAF levels.[7,25,26] Several mechanisms may explain these associations: first, cigarette smoking is a well-known source of exogenous AGEs;[1] second, glycotoxins found in tobacco extracts and tobacco smoke

are able to interact and crosslink rapidly with amino groups of proteins and thus enhance the endogenous formation of AGEs;[27] finally, long-term exposure to cigarette smoke has been linked with increased oxidative stress, systemic inflammation, and endothelial dysfunction.[28]

Another independent determinant of the 1-year increase in SAF observed in this study was HD as first dialysis modality. It is well known that the dialysis procedure itself (HD or PD) exacerbates oxidative stress and systemic inflammation;[29] however, several studies have shown that persons receiving HD have higher levels of biomarkers of oxidative stress, including markers of glycoxidation, protein oxidation, lipid peroxidation, and DNA oxidative damage, as well as higher levels of proinflammatory markers, such as CRP, interleukin-6, and tumor necrosis factor-α, in comparison with persons performing PD.[30] Moreover, dialysis-induced losses of antioxidants are higher in HD than in PD, and endogenous antioxidant activity is significantly suppressed in HD compared with PD.[30] In addition, residual renal function (RRF) declines faster in persons with CKD starting dialysis on HD versus PD,[31] and it has been previously reported that the better preservation of RRF in PD is independently associated with decreased levels of oxidative stress.[32]

Arsov *et al.*[13] reported in univariable analysis that lower dietary AGE intake and lower energy intake were associated with a 1-year increase in SAF in a HD population but that a BMI lower than or higher than 24 kg/m^2 was the sole independent predictor of this observed change; however, chronological age and smoking status, known predictors of SAF, were not included in the multivariable model. Moreover, although BMI is considered a key anthropometric measure of nutritional assessment in persons receiving dialysis,[21,33] it is a poor marker of malnutrition when used in isolation because it can be confounded by overhydration; it does not differentiate between muscle and fat mass; and its interpretation can be influenced by age, gender, and muscle mass.[34] Nongnuch *et al.*[14] reported that lower serum albumin is related to the 1-year increase in SAF in persons receiving HD and that following a vegetarian diet (which is low in dietary AGEs) is independently associated with a stable SAF over 1 year; however, smoking status was also not included in the multivariable analysis, and, similar to the study by Arsov *et al.*,[13] SAF was only measured at 2 different time points (baseline and 12 months), meaning that both studies are subject to the problem of regression to the mean, which may lead to inaccurate conclusions about the determinants of the change in SAF.

Limitations of this study include its observational design, which allowed us to report only associations that do not necessarily imply causal relationships among risk factors and the rate of change in SAF over 1 year. Nevertheless, the associations from our longitudinal study provide more robust evidence than previous cross-sectional analyses. Also, not all dialysis participants had SAF measured at 12 months owing to death, transplantation, or loss to follow-up, which may have led to some selection bias. However, only 20 of 137 participants did not have SAF assessed at 12 months, and the most common reasons were death (11 of 20) and transplantation (7 of 20). Given that SAF is a risk factor for death in the dialysis population, it is likely that those who died would have had higher SAF. This was a single-center study, and results may therefore not be directly applicable to patients from other centers. The results require confirmation in larger multicenter studies. Finally, persons with dark skin color were excluded from our study, and the findings may therefore not be applicable to populations with darker skin colors.

In conclusion, we found in this prospective study that SAF increases over time in most persons receiving dialysis. Prevalence and/or development of malnutrition over 1 year, current smoking, and HD as first dialysis modality were independent determinants of increasing SAF. The relative lack of association with other risk factors implies that SAF is a unique risk marker in the dialysis population. Strategies to reduce or prevent the rise in SAF, including prevention or treatment of malnutrition, should be investigated in prospective studies.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

STROBE Checklist.

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