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CLINICAL RESEARCH

Prospective Study of Change in Skin Autofluorescence Over Time and Mortality in People Receiving Hemodialysis

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Introduction: Elevated skin autofluorescence (SAF), a measure of tissue accumulation of advanced glycation end products (AGEs), is a strong predictor of all-cause and cardiovascular mortality in the hemodialysis population. However, prospective studies investigating the association between changes in SAF over time and mortality are scarce. We therefore aimed to investigate the prognostic value of SAF trend for predicting mortality in a hemodialysis population.

Methods: We enrolled 120 patients on hemodialysis in a 5-year observational, prospective study. SAF was measured at baseline, 3, 6, 9, 12, and 24 months. Rate of change in SAF (i.e., SAF trend) was calculated using linear regression. Time to event was the number of days from baseline to death, kidney transplantation, or March 31, 2022.

Results: Mean age, mean baseline SAF, and median SAF trend were 65 $\pm$ 14 years, 3.4 $\pm$ 0.9 arbitrary units (AU), and an increase of 0.1 (−0.1 to 0.4) AU/yr, respectively. Median observation time was 42 months, during which 59 participants (49%) died. Univariable analysis identified age, history of smoking, lower serum albumin, higher baseline SAF, and increase in SAF as significant predictors of higher mortality. In multivariable analysis, higher baseline SAF (hazard ratio: 1.45; 95% confidence interval: 1.08–1.94; $P = 0.01$) and increasing SAF trend (2.37 [1.43–3.93]; $P < 0.001$) were independent predictors of increased mortality.

Conclusion: An increasing SAF trend and higher baseline SAF were independent predictors of all-cause mortality in this hemodialysis population, suggesting that monitoring of SAF may have clinical utility. Strategies to improve outcomes by reducing or preventing the increase in SAF should now be investigated in prospective studies.

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Hemodialysis is the most common type of kidney replacement therapy worldwide. However, mortality among patients on hemodialysis remains unacceptably high due, in large part, to increased cardiovascular disease.[1] Systemic inflammation and oxidative stress are frequent complications that synergistically contribute to the development of cardiovascular disease and may increase the risk of mortality in this patient population.[2]

AGEs are a group of compounds formed by the nonenzymatic glycation of proteins, lipids, or nucleic acids, which progressively disrupt protein structure, ultimately affecting tissue structure and function. AGE formation in the body is increased by exposure to high glucose levels (in diabetes) and by systemic inflammation and oxidative stress. In addition, AGEs can originate from exogenous sources, including food and tobacco smoke.[3,4] AGEs are cleared in part by renal excretion and therefore classified as uremic toxins, which are markedly increased in people receiving hemodialysis due to increased production, impaired excretion, and inefficient removal.[3] Tissue AGE accumulation can be assessed using a noninvasive technique called SAF, which has been proposed to be a measure of cumulative metabolic stress.[5]

Several observational studies have previously investigated the association between higher baseline SAF measurements and increased mortality in the hemodialysis population.[6–11] In a 3-year prospective

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study, Meerwaldt *et al*.[6] were the first to observe that increased baseline SAF levels independently predicted a 4-fold increase in all-cause mortality, with cardiovascular disease being the main cause of death. However, a single time-point measurement of SAF fails to consider the association of the survival outcome with the change in SAF during the follow-up period.

An increase in SAF between 2 measurements over 12 months has been reported to predict higher mortality among patients on hemodialysis[12]; however, this observation is impacted by the statistical phenomenon known as regression to the mean (i.e., those participants with low values at baseline would likely have higher values on repeat measurement, and vice versa). Therefore, we conducted an observational, prospective study during which SAF was measured at multiple time points over 24 months to derive a robust trend over time; and aimed to investigate the prognostic value of increase in SAF for predicting mortality in a hemodialysis population.

METHODS

Study Population

This was a single-center, prospective, observational study conducted in the Department of Renal Medicine, Royal Derby Hospital, UK. We enrolled 120 hemodialysis patients from September 2016 to August 2017, who were prospectively followed-up for up to 5 years. Participants on hemodialysis who were aged ≥18 years, dialyzed at least 3 times per week for 3 to 4 hours using high-flux biocompatible dialyzers and had an expected survival of more than 1 year were eligible. The exclusion criteria included pregnancy or intended pregnancy, breastfeeding, and hospitalization at the time of recruitment. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the local Research Ethics Committee (East Midlands – Nottingham 1. REC reference: 16/EM/0243). Written informed consent was obtained from all participants.

Data Collection

Data on baseline demographic characteristics, including age, sex, and ethnicity, as well as dialysis vintage (i.e., time since first dialysis treatment), dialysis adequacy (Kt/V), routine blood results, presence of diabetes (defined by clinical diagnosis), cardiovascular disease, postdialysis weight, body mass index, and history of smoking (i.e., current and exsmokers) were collected from electronic medical records and/or direct interviews. Presence of cardiovascular disease was defined by at least 1 of the following events or diagnoses before the baseline SAF measurement: myocardial infarction, cerebrovascular disease or stroke, heart failure, coronary artery disease or surgery, and ischemic heart disease.

Electronic medical records were also used to obtain dates and causes of death, which were classified according to the International Classification of Diseases coding criteria into the following groups[13]: cardiovascular, infection, malignancy, treatment withdrawal, and other cause of death. The classification was performed independently by 2 consultant nephrologists (NMS and MWT) and any disagreements were resolved by discussion. Survival time was defined as the number of days between the baseline assessment and the date of death, censoring due to kidney transplantation, or March 31, 2022.

SAF Measurement

A validated autofluorescence reader version 2.4.3 (AGE Reader, DiagnOptics, Groningen, the Netherlands) was used to measure SAF. The method for measuring SAF is described in more detail elsewhere.[11,14] It has been previously demonstrated that SAF readings have good reproducibility and repeatability (i.e., coefficient of variation of 7%–8%).[15] In brief, the AGE Reader shines an ultraviolet excitation light (intensity of 300–420 nm) on a skin area of the volar surface of the forearm at ∼10 cm below the elbow. The AGE Reader then measures the amount of emitted light that is reflected back from the skin (intensity of 300–600 nm) using a spectrometer and a 200 μm glass fiber. SAF is calculated as the ratio between emission and excitation and is expressed as AU. Three SAF readings were conducted on the nonfistula arm and within the first hour of hemodialysis treatment. The mean value of 3 SAF readings was used for statistical analyses.

SAF was measured at baseline, 3, 6, 9, 12, and 24 months. The rate of change of SAF among these 6 time points (i.e., SAF trend) was then calculated by fitting a regression line using the SLOPE function in Microsoft Excel 2016, where the y-axis represented SAF values and the x-axis represented time points.[16]

The reliability of SAF measurements is compromised in people with dark skin types (Fitzpatrick class V–VI) and skin reflectivity <6% due to increased absorption of excitation and emission lights by skin constituents such as melanin. Therefore, people with dark skin color were not eligible to participate in this study.[17,18]

Statistical Analyses

SPSS version 28.0 (IBM Corporation, Chicago, IL) was used for data management and to perform all statistical analyses. Data are presented as mean ± SD, median (interquartile range), percentages or hazard ratios (95% confidence interval), as appropriate. Missing data were

omitted as follows: C-reactive protein, $n = 7$; SAF trend, $n = 5$. Comparisons of continuous variables between 2 independent groups (e.g., survivors vs. nonsurvivors) were performed using t test or Mann-Whitney U test, whereas intergroup comparisons for categorical variables were conducted with χ^2 test or Fisher exact test. Spearman's correlation coefficient was used to determine the significance and strength of associations between continuous variables.

Cox proportional hazards models were used to investigate the prognostic value of SAF trend (i.e., the rate of change in SAF per year) as a continuous variable for predicting all-cause mortality. Due to the number of events (i.e., deaths), a maximum of 6 variables was included in the model. Predictor variables were selected on the basis of a *P-value* of <0.1 on univariable analysis or biological plausibility (e.g., age and diabetes). Because the distribution of C-reactive protein was highly skewed, this variable was natural log transformed for analysis. Collinearity between predictor variables was checked using Pearson's correlation coefficient. All predictors had a correlation coefficient of ≤0.318; therefore, there was no collinearity among the variables. The proportional hazards assumption was tested by using time-dependent covariates, which were generated by creating interactions of the predictors and a function of survival time, and then were included in the model. The proportional hazards assumption was satisfied because none of the time dependent covariates was significant. In a sensitivity analysis, we repeated the Cox proportional hazards model with SAF trend converted into a categorical variable (i.e., stable/decreasing SAF vs. increasing SAF).

Sample size determination was originally performed for an observational study investigating the association of the interaction between baseline SAF and malnutrition with all-cause mortality as the primary outcome.[10] However, a retrospective sample size calculation showed that with a sample size of 120 participants the analysis would hypothetically have had 80% power to detect a hazard ration of 1.41, assuming that the total number of events (i.e., deaths) achieved was 59. For all statistical analyses, a *P-value* <0.05 was considered to have statistical significance.

RESULTS

Baseline Characteristics of Study Participants

The mean age of the whole population was 65 ± 14 years. Median dialysis vintage was 31 (interquartile range: 11–71) months. The majority of the participants were male (63%), of White ethnicity (88%), and had a history of smoking (63%). Mean baseline SAF was high at 3.4 ± 0.9 AU compared to the reference value of 2.5 ± 0.6 AU for the age group of 60 to 70 years (Table 1).[19]

Follow-Up Results

Median observation time was 42 (interquartile range: 13–62) months, during which 59 participants (49%) died and 16 (13%) received a kidney transplant. The most common cause of death was cardiovascular (32%) followed by infection (25%), treatment withdrawal (19%), cancer (12%), and other causes of death (12%).

In Table 1, we show the baseline participant characteristics according to survival status. Participants who died had significantly higher SAF levels, longer dialysis vintage, and lower serum albumin compared to those who did not die. Those with a history of smoking were also more likely to die. Nonsurvivors had a higher mean age at baseline than survivors. The median number of SAF measurements conducted during follow-up was 6 (interquartile range: 5–6), and with a median observation time between SAF readings of 24 (12–24) months, we observed a median SAF trend showing an increase of 0.1 (−0.1–0.4) AU/yr. However, this varied from a decrease of 0.15 (−0.4–0.0) AU/yr in the stable or decreasing SAF group ($n = 44$ [38%]) to an increase of 0.4 (0.2–0.7) AU/yr in the increasing SAF group ($n = 71$ [62%]). No significant correlations were observed between SAF trend and age, dialysis vintage, Kt/V, postdialysis weight, body mass index, and biochemical variables. SAF trend was not significantly different between males and females, or according to diabetes, cardiovascular disease, smoking, and survival statuses (Table 2).

Univariable Cox regression analysis identified chronological age, history of smoking, lower serum albumin, higher baseline SAF, and an increasing SAF trend as significant predictors of increased mortality. In multivariable Cox proportional hazards analysis, higher baseline SAF (hazard ratio: 1.45; 95% confidence interval: 1.08–1.94; $P = 0.01$) and an increasing SAF trend (2.37, 1.43–3.93; $P < 0.001$) were found to be independent predictors of higher mortality; whereas older age, diabetes, history of smoking and lower serum albumin were not (Table 3). Repeating the Cox proportional hazards model by replacing the continuous variable SAF trend with the categorical variable (i.e., stable or decreasing SAF vs. increasing SAF) did not show a significant association (Supplementary Table S1).

DISCUSSION

In this 5-year prospective observational study, we have found that an increase in SAF over time was an independent predictor of all-cause mortality in this hemodialysis population. We have also confirmed the previously reported independent association between

Table 1. Baseline participant characteristics by survival status

Variable	Overall (n = 120)	Nonsurvivors (n = 59)	Survivors (n = 61)	P-value[a]
Age, yr	65 ± 14	69 ± 12	61 ± 15	0.002
Sex, n (%)				0.8
Female	44 (37)	21 (36)	23 (38)	
Male	76 (63)	38 (64)	38 (62)	
Ethnicity, n (%)				0.3
White	106 (88)	54 (92)	52 (85)	
Other	14 (12)	5 (8)	9 (15)	
History of smoking, n (%)				0.02
Yes	75 (63)	43 (73)	32 (52)	
No	45 (37)	16 (27)	29 (48)	
Diabetes, n (%)				0.2
Yes	49 (41)	28 (48)	21 (34)	
No	71 (59)	31 (52)	40 (66)	
Cardiovascular disease, n (%)				0.1
Yes	48 (40)	28 (48)	20 (33)	
No	72 (60)	31 (52)	41 (67)	
Dialysis vintage, mo (IQR)	31 (11–71)	44 (14–75)	22 (5–57)	0.02
Dialysis adequacy (Kt/V)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.4	0.9
Hemoglobin (g/l)	117 ± 13	116 ± 12	118 ± 14	0.4
Serum albumin (g/l)	32.2 ± 4.3	31.0 ± 4.9	33.4 ± 3.3	0.002
C-reactive protein (mg/l)	9 (4–19)	11 (4–28)	8 (4–12.5)	0.09
Total cholesterol (mmol/l)	3.9 ± 1.1	3.8 ± 1.0	4.1 ± 1.2	0.08
Serum creatinine (μmol/l)	618 (495–746)	601 (501–726)	627 (493–758)	0.8
Serum phosphate (mmol/l)	1.57 ± 0.53	1.54 ± 0.48	1.60 ± 0.58	0.6
Serum potassium (mmol/l)	4.8 ± 0.7	4.9 ± 0.6	4.7 ± 0.7	0.2
Serum adjusted calcium (mmol/l)	2.43 ± 0.13	2.42 ± 0.15	2.44 ± 0.12	0.6
Serum iPTH (pg/ml)	291 (177–427)	296 (172–410)	286 (180–468)	0.8
Skin autofluorescence (AU)	3.4 ± 0.9	3.7 ± 0.9	3.1 ± 0.7	<0.001
Postdialysis weight (kg)	79.2 ± 21.7	79.3 ± 24.5	79.0 ± 18.7	1.0
Body mass index (kg/m^2)	27.7 ± 6.6	27.8 ± 7.3	27.7 ± 5.9	1.0

AU, arbitrary units; IQR, interquartile range; iPTH, intact parathyroid hormone.
[a]Nonsurvivors versus Survivors.
Data are expressed as mean ± SD, median (IQR) or percentages, as appropriate.

higher baseline SAF levels and higher mortality. In univariable analysis, older age, lower serum albumin, and a history of smoking were important predictors of higher mortality.

To our knowledge, the association between increase in SAF over time and higher mortality in the hemodialysis population has only been investigated once in a previous prospective observational study.[12] In this study, the 1-year increase in SAF was independently associated with a 2.5-fold increased risk of all-cause mortality over 3 years. In the current study, we also observed that an increasing SAF trend independently predicted 2.4 times higher risk of overall mortality after 5 years of follow-up. However, in the study by Arsov *et al.*,[12] SAF was only measured at baseline and 12 months, meaning that it is subject to the problem of regression to the mean, whereas in our study we measured SAF at 6 different time points to derive a more robust trend over time. This allows us to draw stronger conclusions about the association between increasing SAF trend and higher mortality. In a sensitivity analysis, the categorical variable (stable or decreasing SAF vs. increasing SAF) did not show an independent association with increased mortality, likely due to an increased probability of a type II error associated with dichotomization of data.[20] Our observations about the association of baseline SAF levels and outcomes were in line with previous studies. We observed a 45% higher risk of all-cause mortality for each AU increase in baseline SAF levels; Jiang *et al.*[11] and Gerrits *et al.*[7] reported that each AU increase in baseline SAF levels was independently associated with a 30% and 83% higher risk of overall mortality, respectively.

Hemodialysis as first dialysis modality is an important determinant of the increase in SAF over time[14] and the hemodialysis procedure itself can exacerbate oxidative stress because there is a suppression of endogenous antioxidant activity, as well as an increase in both dialysis losses of antioxidants and production and accumulation of oxidant products.[21] AGEs are formed more rapidly during oxidative stress with the subsequent formation of reactive carbonyl compounds (i.e., carbonyl stress). At this point, AGE synthesis is irreversible, and these uremic toxins will progressively

Table 2. Associations of skin autofluorescence trend in hemodialysis patients

	Hemodialysis (n = 115)	
Factor	**Skin autofluorescence trend (AU/yr)**	***P*-value**
Sex		0.4
Female (n = 41)	0.2 (0.0–0.6)	
Male (n = 74)	0.1 (−0.1 to 0.4)	
Diabetes		0.7
Yes (n = 47)	0.1 (−0.1 to 0.5)	
No (n = 68)	0.2 (−0.1 to 0.4)	
Cardiovascular disease		0.6
Yes (n = 46)	0.1 (−0.1 to 0.5)	
No (n = 69)	0.2 (−0.1 to 0.4)	
Died		0.8
Yes (n = 56)	0.2 (−0.2 to 0.7)	
No (n = 59)	0.1 (0.0–0.4)	
History of smoking		0.9
Yes (n = 74)	0.2 (−0.1 to 0.4)	
No (n = 41)	0.1 (0.0–0.6)	
	Spearman's Rho	*P-value*
Age (yr)	0.022	0.8
Dialysis vintage (mo)	−0.123	0.2
Dialysis adequacy (Kt/V)	−0.051	0.6
C-reactive protein (mg/l)	−0.069	0.5
Hemoglobin (g/l)	0.038	0.7
Serum creatinine (μmol/l)	0.029	0.8
Serum albumin (g/l)	−0.119	0.2
Total cholesterol (mmol/l)	0.108	0.3
Serum adjusted calcium (mmol/l)	0.012	0.9
Serum phosphate (mmol/l)	−0.005	1.0
Serum potassium (mmol/l)	0.039	0.7
Intact parathyroid hormone (pg/ml)	0.007	0.9
Postdialysis weight (kg)	0.179	0.06
Body mass index (kg/m^2)	0.160	0.09

AU, arbitrary units; IQR, interquartile range.

Table 3. Cox proportional hazards analysis showing predictors of overall mortality in people receiving hemodialysis

	Univariable analysis		Multivariable analysis	
Predictor	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Age (yr)	1.03 (1.01–1.05)	0.01	1.02 (1.00–1.05)	0.05
Sex (male vs. female)	1.07 (0.63–1.82)	0.8		
History of smoking (yes vs. no)	2.44 (1.16–5.14)	0.02	1.74 (0.94–3.24)	0.08
Diabetes (yes vs. no)	1.19 (0.71–1.98)	0.5	1.02 (0.59–1.77)	0.9
Cardiovascular disease (yes vs. no)	1.41 (0.84–2.39)	0.2		
Dialysis vintage (mo)	1.00 (0.99–1.00)	0.9		
Dialysis adequacy (Kt/V)	0.95 (0.46–1.97)	0.9		
Baseline skin autofluorescence (AU)	1.50 (1.18–1.90)	0.001	1.45 (1.08–1.94)	0.01
Skin autofluorescence trend (AU/yr)	2.43 (1.43–4.12)	0.001	2.37 (1.43–3.93)	<0.001
Hemoglobin (g/l)	0.99 (0.97–1.01)	0.3		
Serum creatinine (μmol/l)	1.00 (0.99–1.00)	0.8		
Serum potassium (mmol/l)	1.18 (0.82–1.68)	0.4		
Serum phosphate (mmol/l)	0.84 (0.51–1.38)	0.5		
Serum adjusted calcium (mmol/l)	0.61 (0.09–4.38)	0.6		
Serum albumin (g/l)	0.92 (0.87–0.97)	0.002	0.96 (0.90–1.02)	0.2
Log C-reactive protein (mg/l)	1.45 (0.86–2.45)	0.2		
Total cholesterol (mmol/l)	0.85 (0.66–1.11)	0.2		
Intact parathyroid hormone (pg/ml)	1.00 (0.99–1.00)	0.9		
Postdialysis weight (kg)	1.00 (0.99–1.01)	0.9		
Body mass index (kg/m^2)	1.00 (0.96–1.04)	0.9		

AU, arbitrary units; CI, confidence interval; HR, hazard ratio.

cross-link with tissue proteins, causing a direct alteration of protein structure and function. Collagen and elastin in the skin and vascular basement membranes are especially susceptible to AGE accumulation and subsequent adverse effects (e.g., increased vascular stiffness and endothelial dysfunction). AGEs also interact with specific AGE receptors that lead to the activation of systemic inflammation by increasing the release of proinflammatory cytokines and, consequently, exacerbate tissue damage.[2] Therefore, this tissue damage from cumulative metabolic stress may partially explain the independent association between higher mortality and higher baseline SAF values as well as increasing SAF trend.

It is well known that diabetes, history of smoking, hypoalbuminemia, and older age are independent determinants of increased SAF[22]; as well as independent predictors of increased mortality in the hemodialysis population.[23–26] Nevertheless, in multivariable analysis, we observed that none of these risk factors were independently associated with higher mortality. One explanation is that a causative link between these factors and mortality is metabolic stress that is captured by SAF measurement. Alternatively, this may be due to sample size or to the more pronounced role of SAF as a marker of cumulative metabolic stress in people receiving hemodialysis. In addition, the fact that we did not find any significant associations between SAF trend and other risk factors (e.g., dialysis vintage, diabetes, cardiovascular disease, smoking, C-reactive protein, and serum creatinine), indicates that SAF trend is a unique risk biomarker in the hemodialysis population.

Our findings should be interpreted in the light of some limitations. First, this was a single-center study, and the sample size was relatively small, which prevented us from including more covariates in the multivariable Cox proportional hazards model; and therefore, residual confounding from unmeasured factors cannot be excluded. Second, this study was observational in design, and we were, therefore, unable to assess causality; however, our results suggest

that the risk of death is considerably higher among those subjects with an increase in SAF over time. Finally, SAF measurements are only reliable in people with Fitzpatrick skin types 1 to 4; thus, our findings may not be applicable to people with dark skin types. This is a significant barrier to clinical application and a technical solution will have to be found to enable equitable implementation. Despite these limitations and unlike previous cohorts, the present study is the first to robustly assess trend of SAF over time and to identify increasing SAF trend as an independent risk factor for higher all-cause mortality in a hemodialysis population.

In conclusion, in people receiving hemodialysis, an increase in SAF over time as well as higher baseline SAF levels were independent predictors of higher all-cause mortality compared to other known risk factors. Our observations suggest that regular monitoring of SAF may have clinical utility for risk stratification, though solutions need to be found to make the technique applicable to all skin types. Further, our observations suggest that interventions to decrease SAF or prevent an increase in SAF over time may result in improved survival. This hypothesis should now be tested in prospective trials.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Cox proportional hazards analysis showing predictors of overall mortality in people receiving hemodialysis using skin autofluorescence trend as a categorical variable.

STROBE Statement. Checklist for cohort studies.

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