The association of nutritional factors and skin autofluorescence in persons receiving hemodialysis

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Abstract word count: 266

Manuscript word count: 3062

Short title: malnutrition and skin autofluorescence in hemodialysis patients

ACKNOWLEDGEMENTS

We express our gratitude to all dialysis participants who took part in this study. We thank the research nurse Kelly White for helping with recruitment and collection of data.

SUPPORT AND FINANCIAL DISCLOSURE DECLARATION

The authors declare no conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format. Research study approved by

the local Research Ethics Committee (East Midlands – Nottingham 1. REC reference: 16/EM/0243).

ABSTRACT

Objective: Advanced glycation end-products (AGEs) are uremic toxins that result from hyperglycemia, oxidative stress and systemic inflammation. AGEs are also formed in food during cooking. On the other hand, malnutrition may contribute to AGE formation through its association with oxidative stress and inflammation. AGE accumulation can be measured by skin autofluorescence (SAF) and elevated SAF is independently associated with higher mortality on hemodialysis (HD). We aimed to investigate associations between SAF, dietary AGE intake and markers of malnutrition in persons receiving HD.

Design and setting: single center cross-sectional study.

Subjects: 120 participants on HD dialyzing at least three times per week for 3-4 hours.

Main outcome measures: SAF was measured using an Autofluorescence Reader. Dietary AGE, energy, protein and fat intake, handgrip strength (HGS), anthropometric measurements and biochemistry were also assessed. Subjective Global Assessment was performed to evaluate nutritional status.

Results: SAF was higher in malnourished participants and correlated negatively with serum albumin and cholesterol, HGS and energy, protein and fat intake and positively with C reactive protein and chronological age; SAF did not correlate with dietary AGE intake. Multivariable linear regression analysis showed that diabetes, smoking, serum albumin, HGS, protein intake and dialysis vintage were independent predictors of increased SAF.

Conclusions: Markers of malnutrition were more important determinants of increased SAF than high dietary AGE intake in this HD population. Nutritional interventions aiming to reduce SAF by correcting malnutrition should therefore be investigated. The observed association between higher SAF and malnutrition may in part explain the previously reported association between higher SAF and mortality on HD.

Keywords: skin autofluorescence; advanced glycation end-products; malnutrition; hemodialysis.

INTRODUCTION

Advanced glycation end-products (AGEs) are uremic toxins that are markedly increased in persons on dialysis [1] and may contribute to the pathogenesis of accelerated cardiovascular disease in this population. Accumulation of AGEs in the skin can be assessed by measuring skin autofluorescence (SAF) and previous studies have found that SAF is elevated in persons receiving hemodialysis (HD) [2, 3]. Moreover, higher SAF is independently associated with all-cause and cardiovascular mortality in the dialysis population [4-6], but the mechanism underlying this association is not completely understood. AGEs form cross-links with tissue proteins, particularly collagen in the skin and vascular basement membranes, causing increased arterial stiffness and endothelial dysfunction which may contribute to the pathogenesis of cardiovascular disease. Additionally, AGEs interact with specific AGE receptors that lead to the activation of systemic inflammation, exacerbating tissue damage [1].

AGEs are formed by the non-enzymatic reaction of reducing sugars with free amino groups of proteins, lipids and nucleic acids [7]. AGEs are also formed more rapidly during oxidative stress with the subsequent formation of reactive carbonyl compounds (i.e. carbonyl stress). Hyperglycemia due to diabetes (a common cause of end-stage renal disease [ESRD]) and interaction of blood with the HD membrane have also been identified as contributors to the increased endogenous formation of AGEs in persons on dialysis [7]. Furthermore, AGEs are normally removed from the plasma by renal excretion and those with ESRD are therefore at further risk of AGE accumulation due to decreased excretion [8, 9].

Additionally, AGEs may enter the body from exogenous sources including cigarette smoke or food [1]. AGEs are found naturally in animal-derived and high fat uncooked foods. Importantly, the AGE content of food is increased considerably by cooking methods that require high temperatures such as frying, roasting and grilling. Furthermore, processing of

food accelerates the formation of new AGEs [10]. It has been reported that ~10% of the ingested AGEs are absorbed [11] and studies in healthy, obese and diabetic participants have reported that higher dietary AGE intake is associated with increased serum AGE levels [12-14]. It is unknown whether dietary AGE intake contributes significantly to skin accumulation of AGEs in persons on dialysis.

Malnutrition is one of the most important and frequent complications in persons with ESRD undergoing dialysis [15] and may result from decreased dietary nutrient intake due to loss of appetite, presence of comorbidities, metabolic derangements and other factors associated with uremic toxicity [16]. Additionally, inflammation and oxidative stress (other common conditions in the dialysis population) may further contribute to the development of malnutrition, creating a vicious cycle [17].

Whilst several factors associated with increased SAF have been described in the dialysis population, there are no studies that have examined the effect of diet. Several factors that lead to malnutrition may theoretically also increase SAF but conversely, increased intake of certain foods with high AGE content could also potentially contribute. We therefore conducted a study to identify the determinants of increased SAF in persons receiving HD with a particular focus on nutritional factors including dietary AGE intake and markers of malnutrition.

MATERIALS AND METHODS

Study population

One hundred and twenty HD participants were enrolled in this single center cross-sectional study. Participants were dialyzed at least three times per week for 3-4 hours with high-flux polysulphone dialyzers. Breastfeeding or pregnant women and renal transplant recipients

were excluded. All participants gave written informed consent and ethical approval was granted by the local Research Ethics Committee.

Data collection

Relevant participant characteristics were extracted from electronic medical records and from a self-report questionnaire including demographic characteristics, educational level, occupation status, duration of nephrology care, dialysis vintage, dialysis adequacy, current co-morbidities, history of cardiovascular disease and smoking status. Routine bloods/laboratory tests were also recorded. Diabetes was defined by clinical diagnosis. Duration of nephrology care and dialysis vintage were defined as time since first contact with the nephrology department and time since first dialysis treatment, respectively.

Skin autofluorescence measurement

Tissue AGE accumulation was assessed by measuring SAF using a validated Autofluorescence Reader (AGE Reader, DiagnOptics, Groningen, The Netherlands). The method has been previously described by Meerwaldt et al. [4] Briefly, the AGE Reader shines ultraviolet light on a skin area of ~1 cm^2, protected from surrounding light, with an excitation light range of 300-420 nm (maximum intensity at 370 nm). Emitted light from the skin in the range of 300-600 nm is measured with a spectrometer using a 200- µm glass fiber. SAF is calculated in arbitrary units (AU) by dividing the average emitted light per nm (i.e. fluorescent light coming from the skin) in the range between 420 and 600 nm by the average excitation light intensity per nm in the range between 300 and 420 nm. For each participant, three measurements were performed on the volar surface of the lower arm at approximately 10 cm below the elbow, ensuring that the area had normal skin without visible vessels, scars, tattoos or other abnormalities. Only the non-fistula arm was used, and readings were undertaken within the first hour of HD treatment. Skin color and pigmentation may affect

SAF measurements. Due to the high absorption of the excited light in persons with very dark skin (i.e. skin reflectivity below 6%) [18], SAF might not be reliable in this population and persons with dark skin (i.e. Fitzpatrick skin color type V-VI) were therefore excluded. If the skin reflectivity is <6%, the AGE Reader indicates that the signal is too low to obtain a valid reading. We have previously reported a coefficient of variation of 7-8% for SAF readings [19].

Nutritional assessments

Dietary intake was assessed by means of three 24-hour dietary recalls. Participants were asked to remember all foods and drinks they had the previous day. Average energy, protein and fat intake were calculated by using the software Dietplan 7 (Forestfield Software Limited, West Sussex, United Kingdom). Average daily energy and protein intake were then calculated in kilocalories and grams, respectively, per ideal body weight. A food frequency questionnaire previously validated in diabetic participants [20] was used to assess dietary AGE intake (reported in kilounits/day [kU/day]).

Weight, height, mid-arm circumference (MAC) and triceps skinfold thickness (TSF) were measured according to standard methods as previously described [21]. Body mass index (BMI) was reported in kg/m^2 and mid-arm muscle circumference (MAMC) was calculated by using the following equation: MAMC (cm^2) = MAC – (3.14 * TSF), where MAC and TSF were measured in cm. Handgrip strength (HGS) was measured with the Takei 5401 handgrip digital dynamometer (Takei Scientific Instruments Co., Ltd., Tokyo, Japan). HGS measurement was undertaken within the first hour of HD treatment and the non-fistula arm was used. Ideally a standing position with feet a hip width apart was used for conducting the HGS measurement; when this was not possible, the participant was sitting upright with the arm extended straight down by the side of the bed/chair. The dynamometer's grip range was adjusted until the second joint of the participant's forefinger was bent through 90 degrees.

The participant gripped the dynamometer, exerted full force without letting their arm touch their body and then relaxed.

Nutritional status was assessed by using the 7-point scale Subjective Global Assessment (SGA), which evaluates history of weight loss, dietary intake, gastrointestinal symptoms, functional capacity, disease state/co-morbidities and physical examination, which includes a subjective assessment of subcutaneous fat and muscle mass loss. SGA is a comprehensive and validated nutritional assessment tool [22], widely used in both the clinical and research fields and is recommended by the NKF K/DOQI Nutrition Guidelines [23] as well as the Renal Association Clinical Practice Guideline on Nutrition in CKD [24]. According to the SGA results, the nutritional status can be classified into 3 categories: well-nourished (ratings of 6 or 7 in most categories), mild-moderate malnutrition (ratings of 3 to 5 in at least three categories) and severe malnutrition (ratings of 1 or 2 in at least three categories). For statistical analysis, participants were classified as being well-nourished (SGA score of 6 or 7) or malnourished (SGA scores from 1 to 5).

Statistical analyses

Sample size calculation was performed by using the software nQuery Advanced v8.0 (Statistical Solutions Limited, Boston, Massachusetts). Power calculation showed that with 123 participants (Group 1: n=47; Group 2: n=76) the analysis would have 80% power to detect a significant difference in SAF of 0.5 AU between two groups. This calculation included an inflation of 15% to allow for use of non-parametric tests.

Data management and statistical analyses were performed using the statistical software SPSS version 22.0 (IBM Corporation, Chicago, IL). Data are presented as median (interquartile range [IQR]) or percentages, as appropriate. Intergroup comparisons were performed using Mann

Whitney test for continuous variables and Fisher's exact test for categorical variables. Spearman's correlation coefficient was used to determine the significance and strength of associations between continuous variables. Multivariable linear regression analysis was used to identify independent determinants of AGE accumulation as assessed by SAF. Variables included were all significantly associated with SAF in univariable analysis. A p-value less than or equal to 0.05 was considered to have statistical significance.

RESULTS

Study population characteristics

Baseline characteristics of participants receiving HD are shown in Table 1. Median age, dialysis vintage and SAF were 65 (IQR 54 to 75) years, 31 (11 to 71) months and 3.3 (2.8 to 3.8) AU, respectively. The majority of the participants were male and of white ethnicity. Prevalence of diabetes, malnutrition and coronary heart disease was 40%, 38% and 42%, respectively. Median dietary AGE intake was high at 12384 (8665 to 16984) kU/day, while energy and protein intake were low compared to the recommendations for dialysis patients[23, 24].

Factors associated with dietary AGE intake

Table 2 summarizes associations with dietary AGE intake in HD participants. Malnourished participants had significantly lower dietary AGE intake than those who were well-nourished. Dietary AGE intake correlated significantly and positively with other measures of dietary intake including energy, protein and fat intake, as well as HGS, hemoglobin, serum creatinine and serum phosphate. Participants with educational qualifications and a history of smoking (i.e. former and current smokers), as well as males had higher dietary AGE intake than participants with no educational qualifications, non-smokers and females, respectively.

Determinants of skin autofluorescence

Table 3 shows the determinants of SAF in univariable analyses. Malnourished participants had significantly higher SAF levels than those who were well-nourished and there were significant and negative correlations between SAF and several markers of malnutrition including serum albumin, cholesterol and urea, as well as HGS and energy, protein and fat intake. Furthermore, SAF correlated significantly and positively with CRP, chronological age and dialysis vintage. Persons with diabetes, peripheral vascular disease (PVD) and a history of smoking had also higher SAF levels than those without diabetes or PVD and non-smokers, respectively. Of note, SAF levels were not significantly correlated with dietary AGE intake in this HD population.

Multivariable linear regression identified diabetes, dialysis vintage, history of smoking (current or previous), lower serum albumin, lower HGS and lower protein intake as independent determinants of increased SAF levels, but chronological age was not. The adjusted R^2 for the model was 0.366 (Table 4).

DISCUSSION

We have found that elevated SAF was not positively associated with dietary AGE intake in persons on HD but was associated with several markers of malnutrition, suggesting that malnutrition is a more important determinant of increased SAF than AGE ingestion in this population. We have also confirmed previously reported associations between elevated SAF and diabetes, dialysis vintage, smoking and markers of inflammation.

Dietary AGE intake was high in our study population at 12384 kU/day compared to the suggested intake of less than 8000 kU/day [25]. Other studies conducted in persons receiving HD have also found a dietary AGE intake >12000 kU/day [26]. In our study, the lack of

association between higher SAF and dietary AGE intake in persons on HD was an unexpected finding. This is most likely explained by the positive association between dietary AGE intake and the intake of all dietary components including total energy, protein and fat (high fat and high protein animal-derived foods have a high AGE content) [10]. Serum creatinine and serum phosphate were also positively correlated with AGE intake; this might be explained by the fact that serum creatinine is a marker of protein intake [27] and high protein foods are also high in phosphate [28]. Thus, persons with lower dietary AGE intake also had lower total nutritional intake and were more likely to be malnourished (Table 2). Furthermore, our observation that higher SAF correlated significantly and negatively with several markers of malnutrition (i.e. serum albumin, HGS, total energy, protein and fat intake) and that SAF was independently and negatively associated with serum albumin, protein intake and HGS in multivariable analysis implies that malnutrition may be a more important determinant of elevated SAF in persons receiving HD than dietary AGE intake. Our interpretation is that any impact of dietary AGE intake on SAF was outweighed in this population by the greater impact of malnutrition.

The association between increased SAF and malnutrition may be explained by several mechanisms. The persistent inflammatory state seen in persons with ESRD characterized by increased levels of C reactive protein and pro-inflammatory cytokines (e.g. interleukin-6 and tumor necrosis factor-α), worsens the nutritional status by increasing protein catabolism, muscle wasting and resting energy expenditure, as well as decreasing hepatic protein synthesis (e.g. albumin and pre-albumin) [29]. Furthermore, oxidative stress, another common abnormality in persons on dialysis, is closely linked with systemic inflammation and this interrelationship has been implicated in the development of malnutrition [17]. It has therefore been suggested that a vicious circle of malnutrition, inflammation and oxidative stress accelerates the progression of atherosclerosis and endothelial dysfunction which accounts for

at least some of the increase in cardiovascular mortality risk observed in the dialysis population [15, 17]. In fact, several studies have reported that malnutrition, assessed by the original and modified versions of the SGA, is a strong and independent predictor of mortality in persons receiving dialysis [30-33]. As discussed above, inflammation and oxidative stress may also accelerate AGE formation. It is therefore possible that the previously reported association between increased SAF and higher all-cause as well as cardiovascular mortality in persons on HD may be explained in part by the association between increased SAF and malnutrition that we have observed. Of note, previous studies that have reported an association between higher SAF and mortality in the dialysis population did not assess nutritional status [4-6].

We observed that diabetes, chronological age and dialysis vintage were important determinants of increased SAF. Additionally, higher SAF was found to be more evident in HD participants with a previous history of PVD. Several cross-sectional studies conducted in the dialysis population have also found that presence of diabetes and cardiovascular disease, older age and longer dialysis vintage are associated with higher SAF [3, 34, 35]. It is well-known that cigarette smoking is an exogenous source of AGE formation [7] and in this study, smoking status was found to be an independent determinant of increased SAF. Similar associations with cigarette smoking have been reported in previous studies conducted in healthy participants [36, 37].

The data presented should be interpreted in the light of some limitations. This study was cross-sectional and observational in design and we are therefore unable to confirm a causal relationship between higher SAF and the observed associations. Further longitudinal and interventional studies are therefore required to investigate the relationship between SAF and malnutrition. Nevertheless, this is the first study that has investigated the association of

nutritional factors and tissue AGE accumulation measured by SAF in the HD population. The sample size was relatively small and the study was conducted at a single center. However, we were able to identify robust associations between SAF and nutritional factors that should now be confirmed in larger studies. For technical reasons (discussed in the methods), SAF could not be assessed in persons with darker skin color, who were excluded. Our data may therefore not be applicable to populations with dark skin color.

In conclusion, we have found in this cross-sectional study that factors associated with malnutrition were the most important determinants of higher SAF in persons on HD, but that higher dietary intake of AGEs was not. The observed association between higher SAF and malnutrition may in part explain the previously reported association between higher SAF and mortality on HD. Our findings might have potentially important clinical implications because they suggest that correction of malnutrition may result in a reduction in SAF levels and improved survival. This hypothesis requires testing in further prospective interventional studies.

PRACTICAL APPLICATION

In this study, increased SAF was associated with malnutrition which may partially explain the previously reported association between elevated SAF and higher mortality. Correction of malnutrition may therefore reduce SAF and improve survival, though this hypothesis should be tested in clinical trials before definitive conclusions can be made.

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TABLES

Table 1. Demographic characteristics including clinical, biochemical and nutritional data.

Variable	*Hemodialysis (n=120)*
Age (years)	65 (IQR 54 to 75)
Male [n (%)]	76 (63)
White ethnicity [n (%)]	106 (88)
Qualifications [n (%)]	62 (52)
Unemployed [n (%)]	93 (77)
Current smoking [n (%)]	17 (14)
Diabetes [n (%)]	49 (41)
Malnutrition [n (%)]	46 (38)
Coronary heart disease [n (%)]	51 (42)
Peripheral vascular disease [n (%)]	10 (8)
Duration nephrology care (mo)	98.0 (51.2 to 157.2)
Dialysis vintage (mo)	31.0 (11.0 to 71.0)
Dialysis adequacy (*Kt/V*)[a]	1.2 (1.0 to 1.4)
Hemoglobin (g/L)	119.0 (109.0 to 123.7)
Albumin (g/L)	33.0 (31.0 to 35.0)
C reactive protein (mg/L)	9.0 (4.0 to 19.0)
Total cholesterol (mmol/L)	3.8 (3.1 to 4.5)
Serum creatinine (µmol/L)	618 (495 to 746)
Serum phosphate (mmol/L)	1.48 (1.22 to 1.78)
Serum corrected calcium (mmol/L)	2.43 (2.35 to 2.52)
Serum potassium (mmol/L)	4.7 (4.3 to 5.3)
Skin autofluorescence (AU)	3.3 (2.8 to 3.8)
Dietary AGE intake (kU/day)	12384 (8665 to 16984)
Energy intake (kcal/kg/day)	20.2 (16.5 to 23.8)
Protein intake (g/kg/day)	0.8 (0.6 to 1.0)
Fat intake (g/day)	53.6 (37.3 to 71.5)
Dry weight (kg)	75.2 (64.1 to 92.1)
Body mass index (kg/m^2)	26.2 (23.6 to 31.1)
Handgrip strength (kg)	20.0 (12.4 to 29.0)
Mid-arm muscle circumference (cm^2)	25.5 (23.0 to 28.1)
Triceps skinfold thickness (mm)	15.6 (11.8 to 22.0)

Table 2. Associations of dietary advanced glycation end-product intake in hemodialysis patients.

	Hemodialysis (n=120)	
Factor	*Dietary AGE intake (kU/day)*	*p Value*
Gender		
Female	9765 (8050 to 14095)	0.002
Male	14088 (9719 to 19463)	
Malnutrition		
Yes	11057.8 (8162.1 to 15495.8)	0.049
No	13425.9 (9518.5 to 18760.0)	
Educational qualifications		
Yes	14138 (9814 to 19838)	0.003
No	10934 (8198 to 15022)	
Employed		
Yes	13240 (8594 to 19213)	0.40
No	11784 (8739 to 16404)	
History of smoking		
Yes	13693 (9443 to 18758)	0.02
No	11342 (7546 to 14591)	
	Spearman's Rho	*p Value*
Dialysis vintage (months)	-0.061	0.51
Hemoglobin (g/L)	0.194	0.03
Albumin (g/L)	0.126	0.17
C reactive protein (mg/L)	-0.053	0.57
Total cholesterol (mmol/L)	0.104	0.26
Serum creatinine (µmol/L)	0.303	0.001
Serum phosphate (mmol/L)	0.260	0.004
Energy intake (kcal/kg/day)	0.276	0.002
Protein intake (g/kg/day)	0.320	<0.0001
Fat intake (g/day)	0.340	<0.0001
Body mass index (kg/m^2)	-0.010	0.91
Handgrip strength (kg)	0.268	0.004
Mid-arm muscle circumference (cm^2)	0.129	0.16

Table 3. Determinants of skin autofluorescence in univariate analysis in hemodialysis patients.

	Hemodialysis (n=120)	
Factor	*Skin autofluorescence (AU)*	*p Value*
Malnutrition		
Yes	3.7 (2.8 to 4.1)	0.04
No	3.2 (2.7 to 3.7)	
Diabetes		
Yes	3.6 (3.1 to 4.3)	0.001
No	3.2 (2.7 to 3.7)	
Peripheral Vascular Disease		
Yes	4.0 (3.5 to 5.2)	0.006
No	3.2 (2.7 to 3.8)	
Gender		
Female	3.4 (2.8 to 3.9)	0.90
Male	3.2 (2.7 to 3.8)	
Smoking		
Current	3.7 (2.8 to 3.9)	0.82
Former	3.4 (2.9 to 3.9)	
History of smoking		
Yes	3.4 (2.9 to 3.9)	0.021
No	3.0 (2.6 to 3.7)	
Employed		
Yes	3.4 (2.8 to 3.9)	0.07
No	3.0 (2.5 to 3.3)	
	Spearman's Rho	*p Value*
Age (years)	0.237	0.009
Dialysis vintage (months)	0.236	0.01
C reactive protein (mg/L)	0.273	0.003
Hemoglobin (g/L)	-0.096	0.29
Urea (mmol/L)	-0.203	0.03
Serum creatinine (µmol/L)	-0.094	0.31
Albumin (g/L)	-0.285	0.002
Total cholesterol (mmol/L)	-0.280	0.002
Serum calcium (mmol/L)	-0.191	0.04
Serum phosphate (mmol/L)	-0.069	0.45
Dietary AGE intake (kU/day)	-0.161	0.08
Energy intake (kcal/kg/day)	-0.349	<0.0001
Protein intake (g/kg/day)	-0.339	<0.0001
Fat intake (g/day)	-0.255	0.005
Body mass index (kg/m^2)	0.106	0.25
Handgrip strength (kg)	-0.338	<0.0001
Mid-arm muscle circumference (cm^2)	-0.084	0.36

Table 4. Multivariable linear regression analysis to identify independent determinants of skin autofluorescence in hemodialysis patients.

Factor	*Unstandardized coefficient (B)*	*Standardized coefficient (β)*	*p Value*
Age (years)	0.001	0.014	0.87
Dialysis vintage (months)	0.003	0.233	0.003
Diabetes (no=0, yes=1)	0.379	0.210	0.009
History of smoking (no=0, yes=1)	0.480	0.261	0.001
Serum albumin (g/L)	-0.041	-0.203	0.016
Handgrip strength (kg)	-0.019	-0.241	0.003
Protein intake (g/kg/day)	-0.534	-0.168	0.038

The seven variables shown were used as independent variables. Adjusted R^2 for the model was 0.366