

Original Article

Skin autofluorescence is associated with renal function and cardiovascular diseases in pre-dialysis chronic kidney disease patients

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Abstract

Background. Tissue accumulation of advanced glycation end-products (AGE) is thought to be a contributing factor to the progression of cardiovascular disease (CVD). Skin autofluorescence, a non-invasive measure of AGE accumulation using autofluorescence of the skin under ultraviolet light, has shown associations with CVD in haemodialysis patients. The present study aimed to evaluate relationships of skin autofluorescence to renal function as well as CVD in pre-dialysis patients with chronic kidney disease (CKD).

Methods. Subjects in this cross-sectional analysis comprised 304 pre-dialysis CKD patients [median age, 62.0 years; median estimated glomerular filtration rate (eGFR), 54.3 mL/min/1.73 m²; diabetes, *n*=81 (26.6%)]. AGE accumulation in skin was assessed by skin autofluorescence using an autofluorescence reader. Relationships between skin autofluorescence, eGFR, CVD history and other parameters were evaluated.

Results. Skin autofluorescence correlated negatively with eGFR (*r* = -0.42, *P*<0.01) and increased as CKD stage advanced. Multiple regression analysis revealed significant correlations of skin autofluorescence with age, presence of diabetes, eGFR and CVD history in CKD patients (*R*² = 30%). Age, male gender, smoking history, skin autofluorescence and eGFR were significantly correlated with CVD history, and multiple logistic regression analysis identified age [odds ratio (OR), 1.09; 95% confidence interval (CI), 1.03–1.15; *P*<0.01], history of smoking (OR, 6.50; 95% CI, 1.94–21.83; *P*<0.01) and skin autofluorescence (OR, 3.74; 95%CI, 1.54–9.24; *P*<0.01) as independent factors.

Conclusions. Tissue AGE accumulation measured as skin autofluorescence increased as GFR decreased and was related to CVD history in CKD patients. Non-invasive autofluorescence readers may provide potential markers for clinical risk assessment in pre-dialysis CKD patients.

Keywords: advanced glycation end-products; autofluorescence; cardiovascular disease; chronic kidney disease

Introduction

Cardiovascular mortality is greater in patients with chronic kidney disease (CKD) than in the general population and is associated with CKD stage [1–4]. As cardiovascular disease (CVD) is the main cause of death in these patients and possesses higher incidence than the development of end-stage renal disease (ESRD) in CKD patients [5], early recognition of CVD and risk stratification is crucial. However, traditional risk factors for CVD such as hypertension, smoking and diabetes mellitus cannot fully explain the high prevalence of CVD in CKD patients [6].

Advanced glycation end-products (AGE), synthesized by the non-enzymatic response of glucose to protein (the Maillard reaction), have been implicated as a contributing factor in the progression of chronic, age-related diseases such as diabetic vascular complications, dialysis-related amyloidosis, Alzheimer's disease, rheumatoid arthritis and atherosclerosis [7–9]. AGE have also been recognized as a CKD-related (non-traditional) risk factor for CVD. In addition to hyperglycaemia and increased oxidative stress, decreases in glomerular filtration rate (GFR) are thought to be an important determinant contributing to the accumulation of AGE. Plasma pentosidine levels reportedly correlate with serum creatinine levels [10] and are markedly elevated in dialysis patients, even in non-diabetic patients [8]. AGE accumulation in arteriosclerotic lesion sites is thought to play an important role in the pathogenesis of chronic complications such as CVD in patients with diabetes [11–13]. Monnier *et al.* reported that tissue autofluorescence is related to AGE accumulation and progression of diabetic complications, after evaluating tissue autofluorescence using skin biopsy specimens [14]. However, skin biopsy is an invasive and time-intensive method and is not feasible in daily practice for outpatients. In addition, serum AGE levels do not reflect tissue AGE contents [15] and do not predict mortality in dialysis patients [16,17].

An autofluorescence reader (AGE Reader; Diagnostix, Groningen, the Netherlands) non-invasively assesses AGE accumulation using skin autofluorescence under ultraviolet light, and skin autofluorescence has been validated against AGE measurements in skin biopsies from the site of skin autofluorescence measurement, performed in patients with ESRD, diabetes and healthy controls [18–20]. Skin autofluorescence is reportedly an independent predictor of cardiovascular mortality in dialysis patients [20] and diabetic patients [21] in Caucasian populations. We have recently reported that skin autofluorescence is independently associated with CVD history in Japanese (non-Caucasian) haemodialysis patients [22]. However, the relationship between skin autofluorescence, renal function and CVD in pre-dialysis CKD patients has not been reported. Therefore, in order to assess the validity of skin autofluorescence in pre-dialysis CKD patients, we investigated the association between skin autofluorescence, CKD stage, CVD history and other clinical risk factors in this cross-sectional analysis.

Materials and methods

Study population

This cross-sectional study included 304 pre-dialysis CKD patients who visited Fukushima University Hospital or Tani Hospital between December 2008 and August 2009. Patients receiving dialysis therapy were excluded from this study. The study protocol complied with the Declaration of Helsinki and was approved by the ethics committees at Fukushima Medical University. All patients received an explanation of the procedures and possible risks of this study and provided written informed consent to participate. All patients were Japanese (non-Caucasian). Patients with acute/chronic inflammatory disease and active malignancy were excluded.

Data collection

Blood pressure was taken as a seated single measurement using an aneroid device, obtained after 5 min of rest. Blood samples were collected at the clinic by venipuncture from every patient in a non-fasting state. Serum creatinine was measured using an enzyme-based method, and serum albumin, haemoglobin, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were measured according to the automated standardized laboratory techniques in the clinical laboratories of each participating institution. Diabetic retinopathy was determined by independent ophthalmologists based on retinal photography, and mean haemoglobin A1c level of the previous year was measured in 81 diabetic patients.

Definition of chronic kidney disease, diabetes and cardiovascular disease

The estimation equation for Japanese patients with CKD was applied for estimation of GFR. This equation calculates GFR from serum creatinine, age and gender using the following formula: [estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²) = 194 × Serum creatinine^{-1.094} × Age^{-0.287} (×0.739 for women)]. This formula has been validated against the GFR measured by using inulin clearance, which is the gold standard for measuring GFR, in Japanese patients [23]. Since this equation estimates GFR more accurately for the Japanese population than the previously reported equations such as the Modification of Diet in Renal Disease Study equation with Japanese coefficient and Cockcroft–Gault equation, the Japanese Society of Nephrology recommends using this equation for GFR estimation for Japanese in clinical practice and for epidemiological study. CKD was defined as eGFR <60 mL/min/1.73 m² or positive dipstick results for proteinuria (≥1+) [24]. Diabetes was defined by glucose values ≥200 mg/dL at any time, fasting glucose values ≥126 mg/dL or the use of insulin or oral hypoglycaemic drugs. A history of CVD was defined if at least one of the following events occurred before the time of skin-autofluorescence measurement: acute myocardial infarction due to clinical and electrocardiographic or laboratory changes;

angina pectoris based on clinical characteristics; coronary artery disease documented by coronary angiography; cerebral infarction verified by computed tomography (CT), magnetic resonance imaging (MRI) and/or the course of neurological disorders; aortic disease including dissection and aneurysm verified by CT and/or MRI; and peripheral artery disease. The definition of peripheral artery disease included patients with intermittent claudication (Fontaine's stage II), ischaemic rest pain (stage III) or ulcer, necrosis or a history of amputation (stage IV).

Skin autofluorescence

AGE accumulation was assessed based on skin autofluorescence using the AGE Reader, as described in detail previously [18,19]. The measure of autofluorescence was defined as the average light intensity per nanometer in the range between 420 and 600 nm, divided by the average light intensity per nanometer in the range between 300 and 420 nm. Autofluorescence was expressed in arbitrary units (AU). The amount of ultraviolet light exposure is small, and the autofluorescence reader has already been tested in several studies without any adverse effects [18–22]. All measurements were performed at room temperature with the patient in a seated position, at the volar side of the lower arm, approximately 10–15 cm below the elbow fold. Care was taken to perform the measurement at a normal skin site, thus without visible vessels, scar, lichenification or other skin abnormalities. The intra- and inter-day assay precision expressed as coefficients of variation for autofluorescence reader measurements were 2.5% (*n*=10) and 4.6% (*n*=12), respectively. Autofluorescence was calculated offline by automated analysis and was observer-independent.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 17.0 software (SPSS Japan, Tokyo, Japan). All variables are expressed as median [interquartile range (IQR)]. Spearman's rank correlation test was used to estimate relationships between variables. Multiple linear regression analysis was performed to determine the independent relationship of variables with skin autofluorescence. Independent effects of variables on CVD were assessed by forward stepwise logistic regression analysis (*P*<0.05 for entry and *P*≥0.10 for removal). Differences were considered significant at the *P*<0.05 level.

Results

Clinical and biochemical characteristics

Table 1 shows the clinical characteristics of the 304 CKD patients. Median age was 62.0 years (IQR, 49.3–73.0 years), and 51.3% of subjects were male. Median titre of skin autofluorescence was 2.07 AU (IQR, 1.75–2.43 AU; range, 0.91–3.90 AU). Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) were being administered to 216 patients (71.1%). History included: CVD in 21 patients (6.9%), ischaemic heart disease in six patients (2.0%), cerebral infarction in seven patients (2.3%), peripheral artery disease in five patients (1.6%) and aortic disease in six patients (2.0%).

Correlations between skin autofluorescence and other parameters in chronic kidney disease patients

Skin autofluorescence was increased as CKD stage advanced [median skin autofluorescence for: stage 1, 1.60 AU (IQR, 1.25–1.95); stage 2, 1.90 AU (IQR, 1.59–2.14); stage 3, 2.23 AU (IQR, 1.89–2.49); stage 4 or above, 2.37 AU (IQR, 2.00–2.78)]. These differences were significant in stage 1 vs stage 2 and stage 2 vs stage 3 (*P*<0.01) and non-significant in stage 3 vs stage 4 or above (*P*=0.08).

Table 1. Clinical characteristics of patients with chronic kidney disease

Variable	CKD patients
N	304
Age (years)	62.0 (49.3–73.0)
Gender (male)	156 (51.3%)
History of smoking	128 (42.1%)
Body mass index (kg/m ²)	23.6 (21.3–26.5)
Diabetes	81 (26.6%)
Systolic BP (mmHg)	132.0 (119.0–147.8)
Diastolic BP (mmHg)	76.0 (68.0–84.0)
Skin autofluorescence (AU)	2.07 (1.75–2.43)
eGFR (mL/min/1.73 m ²)	54.3 (42.7–70.1)
Albumin (g/dL)	3.90 (3.63–4.20)
Haemoglobin (g/dL)	13.1 (11.9–14.2)
LDL cholesterol (mg/dL)	107.0 (89.0–134.0)
HDL cholesterol (mg/dL)	54.0 (46.0–62.0)
CVD history	21 (6.9%)
ACEi or ARB	216 (71.1%)

Values are expressed as medians (interquartile range). CKD, chronic kidney disease; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Determinants of skin autofluorescence in multiple regression analysis

Variable			
Dependent	Independent	β	P
Skin autofluorescence	Age	0.22	<0.01
	Diabetes	0.16	<0.01
	eGFR	−0.18	<0.01
	CVD history	0.14	<0.01

The final result is given in the table. β is the standard coefficient; the multiple coefficient of determination (R^2)=0.30.

Skin autofluorescence did not correlate with gender distribution, history of smoking, body mass index, systolic blood pressure, LDL cholesterol or medication with ACEi or ARB. However, age ($r=0.42$, $P<0.01$), diabetes ($r=0.33$, $P<0.01$), eGFR ($r=-0.42$, $P<0.01$), serum albumin ($r=-0.19$, $P<0.01$), haemoglobin ($r=-0.34$, $P<0.01$), HDL cholesterol ($r=-0.12$, $P=0.04$) and CVD history ($r=0.26$, $P<0.01$) were significantly correlated with skin autofluorescence in CKD patients. Multiple linear regression analysis showed that 30% (R^2) of the variance of skin autofluorescence could be predicted by age, diabetes, eGFR and CVD history (Table 2). Serum albumin, haemoglobin and HDL cholesterol were not significant contributors in this model.

The presence of diabetes was independently and positively associated with skin autofluorescence in CKD patients. We compared skin autofluorescence in patients with and without diabetes. Figure 1 shows skin-autofluorescence value in each category of age and eGFR. Skin-autofluorescence titre was elevated in diabetic patients compared with non-diabetic patients in each age and eGFR category, with significant differences ($P<0.05$) in the age categories 51–61, 62–72 and >72 years, but not in the age category <51 years ($P=0.06$), and significant differences ($P<0.01$) in the eGFR categories 60–89 and 30–59 mL/min/1.73 m² but not in the ≥ 90 - and <30-mL/min/1.73 m² categories.

The age category <51 years included only four patients with diabetes, and the eGFR ≥ 90 mL/min/1.73 m² category included only two patients with diabetes.

In patients with diabetes, skin autofluorescence correlated with serum albumin ($r=-0.43$, $P<0.01$), haemoglobin ($r=-0.38$, $P<0.01$), presence of diabetic retinopathy ($r=0.35$, $P<0.01$), and CVD history ($r=0.25$, $P=0.02$); eGFR showed a trend toward a correlation with skin autofluorescence, but this was not significant ($P=0.06$). Twenty-five per cent of the variance in skin autofluorescence in diabetic CKD patients could be explained by the independent effects of haemoglobin ($\beta=-0.48$, $P<0.01$), CVD history ($\beta=0.27$, $P=0.01$) and the mean haemoglobin A1c level of the previous year ($\beta=0.24$, $P=0.04$). eAge, GFR and duration of diabetes did not show any independent effects on skin autofluorescence in this sub-group analysis. In patients without diabetes, skin autofluorescence correlated with age ($r=0.40$, $P<0.01$), systolic blood pressure ($r=0.15$, $P=0.02$), eGFR ($r=-0.42$, $P<0.01$), serum albumin ($r=-0.14$, $P=0.04$), haemoglobin ($r=-0.18$, $P<0.01$), HDL cholesterol ($r=-0.14$, $P=0.03$) and CVD history ($r=0.14$, $P=0.04$). Twenty-seven per cent of the variance in skin autofluorescence among non-diabetic patients could be explained by the independent effects of eGFR ($\beta=-0.29$, $P<0.01$), age ($\beta=0.24$, $P<0.01$), and CVD history ($\beta=0.14$, $P=0.03$). CVD history had independent and positive effects on skin autofluorescence in both diabetic and non-diabetic patients.

Comparison of data between patients with and without cardiovascular disease

Skin autofluorescence was 30% higher in patients with CVD history [median, 2.66 AU (IQR, 2.12–3.19)] than in those without [median, 2.05 AU (IQR, 1.71–2.39); $P<0.01$]. Skin autofluorescence had significant effects on CVD in both the diabetic group [odds ratio (OR), 4.26; 95% confidence interval (CI), 1.21–15.04; $P=0.02$] and the non-diabetic group (OR, 5.46; 95%CI, 1.95–15.33; $P<0.01$) (Figure 2), and these effects remained significant after adjustment by age (diabetic group: OR, 3.76; 95% CI, 1.07–13.28; $P=0.03$; non-diabetic group: OR, 3.28; 95%CI, 1.10–9.82; $P=0.03$).

Table 3 shows unadjusted and adjusted ORs for the presence of CVD in CKD patients. Age, male gender, history of smoking, skin autofluorescence and eGFR were significantly related to CVD. Due to the limited sample size, we performed forward stepwise logistic regression analysis using CVD as the dependent variable and identified age, smoking history and skin autofluorescence as independently related to CVD. Male gender and eGFR were still significant factors for CVD after adjustment by age (male: OR, 5.94; 95%CI, 1.87–18.88; $P<0.01$; eGFR: OR, 0.96; 95%CI, 0.94–0.99; $P<0.01$) but were not selected in this multivariable model.

Discussion

This cross-sectional study found that skin autofluorescence increased as CKD stage advanced. CVD history showed

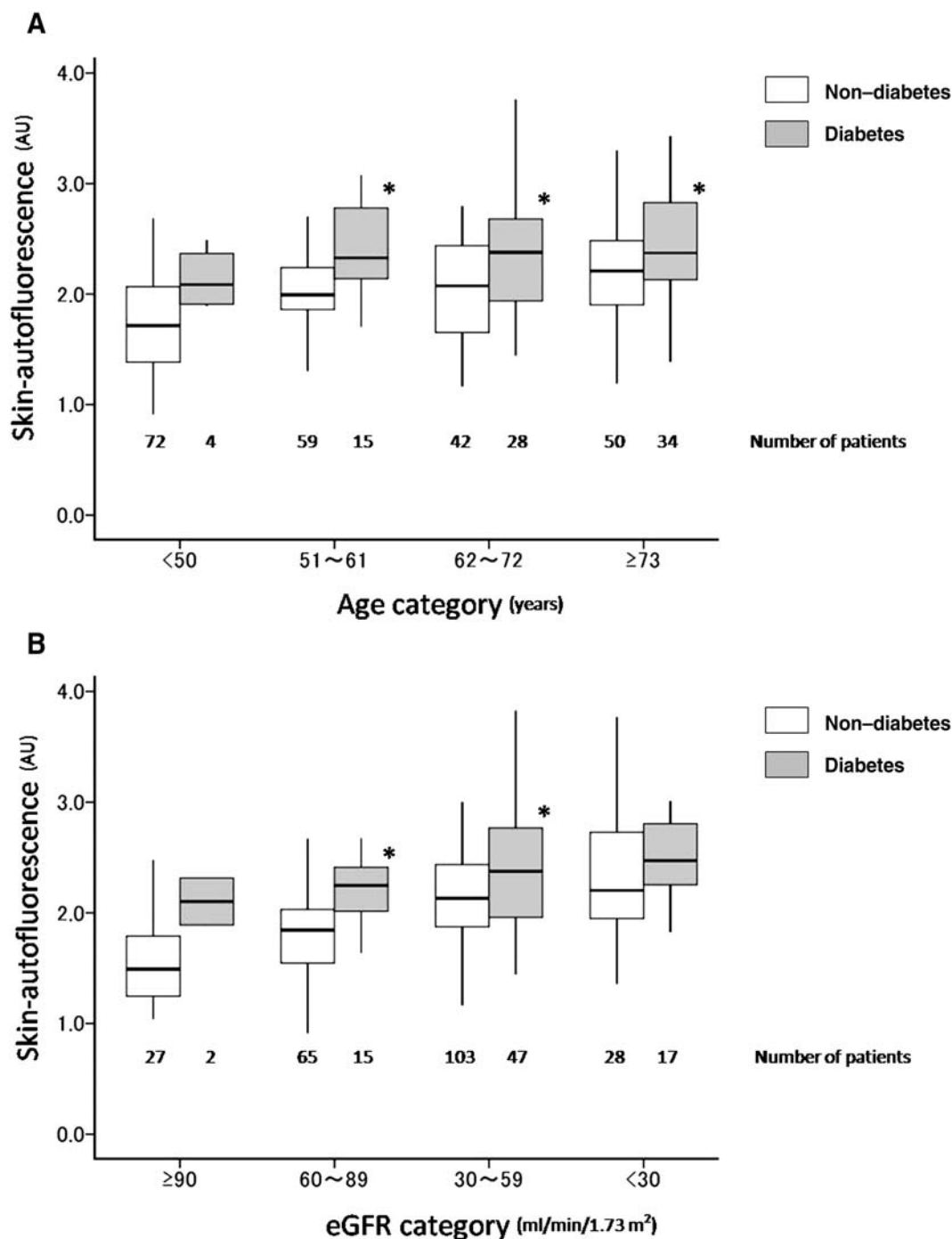


Fig. 1. These boxplots show the distribution of skin autofluorescence in each category of age (A) and eGFR (B) among chronic kidney disease patients with or without diabetes. Age category was divided by quartile of age. * $P < 0.05$ vs non-diabetic patients.

independent effects on skin autofluorescence in both the diabetic and non-diabetic groups. Moreover, skin autofluorescence was higher in patients with CVD than in those without and still showed a significant contribution to CVD in the multivariable logistic regression model that included traditional risk factors for CVD such as age, smoking, blood pressure and diabetes. This study is thus the first to show the independent relationship of skin autofluorescence to renal function and CVD in pre-dialysis CKD patients.

As progression of CVD and AGE accumulation are time-dependent processes, the present results could be biased by age. We always included age as a dependent variable in multivariate analysis to reduce the potential effects of such biases, and our data still showed a significant correlation between skin autofluorescence and CVD.

Reduced GFR is a recognized risk factor for progression of CVD, the prevalence of which increases with decreased GFR [3]. In the present study, eGFR was one of the independent determinants for skin autofluorescence and dis-

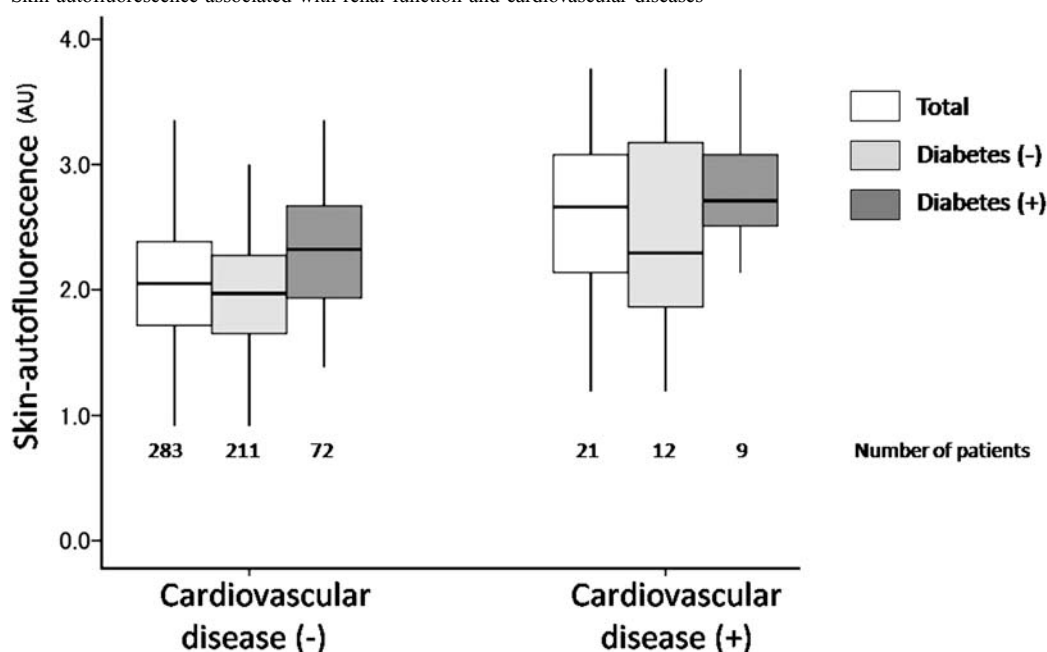


Fig. 2. Skin autofluorescence in patients with or without cardiovascular disease. Skin autofluorescence was significantly higher in patients with cardiovascular disease than in those without, for all chronic kidney disease patients ($P < 0.01$), non-diabetic chronic kidney disease patients ($P < 0.05$) and diabetic patients ($P < 0.05$). Skin autofluorescence was elevated in diabetic patients compared with non-diabetic patients for patients both with and without cardiovascular disease ($P < 0.05$).

played a significant relationship to CVD even after age adjustment. However, eGFR was not selected as an independent factor for CVD in the multivariable logistic regression model. As this study included only a cross-sectional analysis with limited patients, prospective investigation is necessary to evaluate the relationship between eGFR, skin autofluorescence and cardiovascular risk in CKD patients.

Hyperglycaemia is one of the major contributors to AGE accumulation. Previous studies have shown that the presence of diabetes has an independent effect on skin-autofluorescence values in dialysis patients [20,22], and skin autofluorescence was indeed higher in diabetic patients compared to non-diabetic patients in each category of age and eGFR, showing an independent relationship to

the presence of diabetes and glycaemic control in diabetic patients in the present study. Skin autofluorescence is reportedly positively correlated to the severity of diabetic vascular complications and predicts progression of CVD and mortality in diabetic patients [21,25,26]. However, few studies have evaluated skin autofluorescence in non-diabetic CKD patients. We performed sub-analysis in patients with or without diabetes and found that skin autofluorescence exhibited a significant relationship to CVD in both the diabetic and non-diabetic groups even after adjusting for age. Independent determinants of skin autofluorescence were eGFR, age, body mass index and CVD in non-diabetic patients. However, eGFR did not show a significant effect on skin autofluorescence in diabetic

Table 3. Variables related to cardiovascular disease in chronic kidney disease patients by logistic regression analysis

Variables	Univariate			Multivariate		
	OR	95%CI	P	OR	95%CI	P
Age (years)	1.08	1.03–1.13	<0.01	1.09	1.03–1.15	<0.01
Gender (male)	4.40	1.45–13.41	<0.01			NS
History of smoking	6.39	2.10–19.49	<0.01	6.50	1.94–21.83	<0.01
Body mass index (kg/m ²)	1.00	0.90–1.12	0.95			NS
Diabetes	2.20	0.89–5.43	0.09			NS
Systolic BP (mmHg)	1.02	1.00–1.04	0.07			NS
Diastolic BP (mmHg)	1.01	0.98–1.04	0.62			NS
Skin autofluorescence (AU)	5.14	2.40–11.03	<0.01	3.74	1.54–9.14	<0.01
eGFR (mL/min/1.73 m ²)	0.96	0.94–0.98	<0.01			NS
Albumin (g/dL)	0.70	0.41–1.21	0.21			NS
Haemoglobin (g/dL)	0.83	0.67–1.03	0.09			NS
LDL cholesterol (mg/dL)	1.00	0.99–1.01	0.84			NS
HDL cholesterol (mg/dL)	0.97	0.93–1.00	0.06			NS

NS, not significant.

patients. This may reflect that decreased GFR has a greater contribution to AGE accumulation in non-diabetic patients than in diabetic patients.

ACEi and ARB reportedly reduce AGE formation [27], but medication with these agents had no significant correlation with skin autofluorescence in the present cross-sectional analysis. Evaluation of whether these drugs reduce AGE accumulation and whether skin autofluorescence represents a possible surrogate marker for the effects of these treatments in prospective investigations is both necessary and interesting.

Several limitations to the present study must be considered. First, skin-autofluorescence measurements are affected by skin colour and pigmentation and are not reliable for patients with very dark skin due to the high absorption grade of excited light [18,28,29]. The autofluorescence reader has not been sufficiently validated for non-Caucasian (Japanese) patients at present, but skin autofluorescence has been reported to be strongly correlated with AGE accumulation in evaluations assessed by skin biopsy specimens among Caucasian patients with diabetes and ESRD, despite the fact that hyperpigmentation is one of the frequent skin alterations in ESRD. Several recent studies have presented skin-autofluorescence results in Japanese patients with ESRD [22,30], rheumatoid arthritis, osteoarthritis and dialysis-related spondyloarthropathy [31] and cerebral infarction [32] and suggested that skin autofluorescence has potential as a useful marker in both Caucasian and non-Caucasian subjects. Second, the present study was only a cross-sectional analysis with insufficient size. A prospective investigation with sufficient sample size and better statistical methods is still needed to clarify whether skin autofluorescence is a relevant predictor for the progression of CVD and mortality in patients with CKD.

The importance of assessment for CKD-related (non-traditional) risk factors such as anaemia, malnutrition, inflammation, oxidative stress and AGE accumulation as well as traditional risk factors for CVD is higher in CKD patients. Early detection and intervention for these risks is necessary to prevent CVD. As a non-invasive, convenient instrument, the autofluorescence reader may have a potentially important role to play as a useful tool for assessing cardiovascular risk in daily practice among CKD patients. Early and close screening for CVD in patients with increased skin-autofluorescence value may have a potential to prevent CVD or improve mortality; however, further investigation is still necessary to closely examine whether skin autofluorescence is a relevant marker reflecting AGE accumulation for cardiovascular risk. Recently, some AGE breakers have been reported to inhibit the development of renal and vascular disease on experimental animals. Skin autofluorescence might offer a tool to monitor the effects of treatment as well, when these drugs apply in clinical practice in the future.

Tissue AGE measured as skin autofluorescence is independently related to renal function and CVD history in pre-dialysis CKD patients. Thus, non-invasive autofluorescence readers may have potential for providing useful biomarkers of cardiovascular risk in CKD patients, although prospective investigations are needed to evaluate whether skin autofluorescence predicts progres-

sion of cardiovascular disease or mortality and the therapeutic effectiveness.

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Conflict of interest statement. None declared.

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