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# Accumulation of tissue advanced glycation end products correlated with glucose exposure dose and associated with cardiovascular morbidity in patients on peritoneal dialysis

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## ABSTRACT

**Objectives:** Accumulation of tissue advanced glycation end products (AGEs) is a marker of cumulative glycemic and/or oxidative stress. Cutaneous AGEs levels measured by skin autofluorescence correlate well with cardiovascular outcomes in diabetes and hemodialysis (HD) patients. The present study aimed to compare tissue AGEs levels with peritoneal dialysis (PD) and HD patients and to evaluate the relationship between skin autofluorescence and cardiovascular morbidity in patients on PD.

**Methods:** A total of 2388 maintenance dialysis patients (613 PD and 1775 HD) were enrolled in this cross-sectional study. Skin autofluorescence was measured non-invasively with an autofluorescence reader. Cardiovascular morbidity was defined as clinically diagnosed ischemic heart disease, heart failure, stroke or peripheral vascular disease from initiation of dialysis.

**Results:** More than 90% of patients on both PD and HD had met current dialysis adequacy targets. Compared to HD group, PD patients receiving conventional glucose-containing dialyzate had significantly higher skin autofluorescence values in each category of age and dialysis duration, irrespective of the presence or absence of diabetes. In PD patients, skin autofluorescence values were strongly correlated with the duration of PD and glucose exposure dose and independently associated with cardiovascular morbidity. Multivariate analysis revealed that glucose exposure dose and skin autofluorescence were the strongest risk factors for cardiovascular morbidity in PD patients after adjustment by age, gender, and other classic- or uremic-related risk factors.

**Conclusions:** Accumulation of tissue AGEs provides a potential link between PD exposure of metabolic stress and progression of cardiovascular disease in patients on PD.

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## 1. Introduction

Cardiovascular disease (CVD) is the predominant cause of mortality in patients with end-stage renal disease (ESRD) undergoing dialysis [1,2]. Risk factors for CVD in these patients include those affected the general population and those related to ESRD as

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well as those that are specific to chronic dialysis. It remains of paramount importance to distinguish the contributions of these factors to cardiovascular morbidity and mortality in patients undergoing maintenance dialysis.

Increased genesis and accumulation of advanced glycation end products (AGEs) is common in patients with chronic kidney disease (CKD), and in particular those on chronic dialysis [3–5]. AGEs are protein adducts formed by the Maillard reaction occurring in tissues and in stored glucose solutions (such as those used for peritoneal dialysis) [6]. Hyperglycemia is a sufficient but not necessary condition for accumulation of AGEs [7]. Several factors, such as oxidative and carbonyl stress or reduced renal clearance, all seem to increase the formation of AGEs [8–10]. Accumulation of chemically stable AGEs on long-lived tissue proteins may serve as a marker of cumulative metabolic stress [11–13] and has been implicated in CVD in diabetic, pre-dialysis CKD and hemodialysis (HD) patients [13–17].

Determination of tissue accumulation of AGEs is an invasive and expensive procedure, and blood or urine sampling of AGEs does not necessarily reflect tissue level of AGEs [18]. Recently, skin autofluorescence has emerged as a non-invasive and reproducible tool to estimate the AGEs level of skin tissue. Skin autofluorescence has been validated against skin levels of several specific AGEs and a classic assay for collagen-linked fluorescence in patients with different diseases (diabetes, ESRD, and controls) [13,19,20]. Skin autofluorescence was consistently shown to be related to cardiovascular mortality in patients with diabetes and those on HD in different races (Caucasian and Asian) [13,15,16,21].

Cardiovascular disease is the most frequent cause of mortality in patients on maintenance peritoneal dialysis (PD). The high concentration of glucose in the conventional PD solution and the presence of glucose degradation products (GDPs) formed during the manufacturing process, e.g., heat-sterilization, increase the formation of AGEs in peritoneum [22,6]. A recent study, conducted in a cohort including 53 PD patients, showed that skin autofluorescence levels are elevated in PD patients [23]. However, the relationship between tissue AGEs level and CVD in PD patients has not been established. The present study was to test the hypothesis that accumulation of skin AGEs might be linked to increased exposure of glucose during PD and associated with CVD in this population.

## 2. Methods

### 2.1. Study population and data collection

The study cohort consisted of patients enrolled in the China Cooperative Study on Dialysis (CCSD). CCSD is a multi-center cohort study aimed at evaluating the cardiovascular morbidity during chronic dialysis in Chinese patients. The study cohort consisted of all adult (older than 18 years) patients who started maintenance dialysis between January 1, 2005, and December 1, 2010 in the 9 of the largest dialysis facilities (the number of patients on HD  $\geq 200$  or PD  $\geq 100$ ) in 6 cities of China (Beijing, Shanghai, Guangzhou, Hangzhou, Wuhan, and Xian). Among the cohort, 5.6% (HD,  $n = 125$ ; PD,  $n = 8$ ) of patients had been on chronic dialysis before transferred to the selected facility.

Data used in the present study were derived from the database of CCSD. They were collected on the basis of review of medical records of the participants. All records were abstracted by a group of experienced doctors and research nurses. In the present study, the patients who had clinically diagnosed ischemic heart disease, heart failure, stroke, and peripheral vascular disease at initiation of dialysis and those who were on dialysis for less than 3 months were excluded.

Ischemic heart disease was defined as the presence of myocardial infarction, coronary revascularization procedures, angina, and ischemia on electrocardiogram or other diagnostic tests [24]. The diagnosis of heart failure was based on an ejection fraction below 40% or New York Heart Association Criteria grade 3 or more [25]. Peripheral vascular disease was defined as the presence of amputation of digits or extremities secondary to vascular disease, peripheral arterial bypass or angioplasty, intermittent claudication, recurrent cellulitis secondary to vascular disease [26].

A total of 2388 (1775 on HD and 613 on PD) patients were finally analyzed.

### 2.2. Lab test and clinical parameters

Hematology and biochemistry measurements, time-averaged over the latest 3 months, were recorded. Biochemical test was performed by the clinical laboratories in individual dialysis facilities in which the lab standards are nationalized. The inter-facilities variability of biochemical data is ranged from 0.95 to 1.12 [27].

Blood pressure measurement was done by sphygmomanometer and taken before each of the three HD sessions or each of the three PD visits, three times at 1 min intervals, all after 10 min of rest in a supine decubitus position. The mean of the three readings was calculated.

### 2.3. Dialysis regimens

All PD patients used lactate-buffered, 1.36%–3.86% glucose-containing solutions (Baxter) as prescribed for routine clinical care. Patients were followed up every 1–3 months in each center by the fixed staffs. PD glucose exposure dose for each patient was calculated based on PD prescription records expressed as total glucose dose or averaged glucose dose *per week* ( $\Sigma$  glucose dose [gram]/vintage [weeks], where  $\Sigma$  is the total glucose dose used during PD treatment).

Patients maintained on HD were dialyzed twice or thrice weekly with low-flux polysulphone or polyacrylamide dialyzer, either 1.5 or 1.7 m<sup>2</sup> (Fresenius, Germany; Gambro, Sweden; Nipro, Japan; B. Braun, Germany; Langsheng, China). All treatments were of 4-h–5-h duration with conventional glucose-free, bicarbonate-based dialyzate containing 1.25 mM–1.5 mM calcium, 2.0 mM potassium, and 138 mM sodium. Dialyzate flow was 500 mL/min.

### 2.4. Skin autofluorescence measurement

Tissue AGEs measurement was performed for all survived participants of CCSD. It was measured before the latest HD session or PD follow up by using a cutaneous autofluorescence device (AGE Reader, DiagnOptics Technologies, Netherlands) [19,28]. The values were compared with an age-matched non-CKD database contained within the device. The autofluorescence reader illuminates a skin surface of  $\sim 1$  cm<sup>2</sup>, guarded against surrounding light, with an excitation light source between 300 and 420 nm (peak excitation approximately 350 nm). Only light from the skin is measured with a spectrometer in the 300–600-nm range, using a 200- $\mu$ m glass fiber (Farnell, Leeds, UK). All measurements were performed at room temperature in a semi-dark environment before dialysis or during PD clinic consultations. The non-dominant forearm rests on the device, and three readings, all taken within 1 cm of each other away from any areas of bruising or pigmentation, were averaged and recorded. A connected computer analyzed the level of autofluorescence and correlated that to known normal range.

Repeated autofluorescence measurements on 1 day and intra-individual seasonal variance showed an altman error percentage of <6%. The intra- and inter-day assay precision expressed as

**Table 1**  
Clinical and biochemical characteristics of the patients<sup>a</sup>.

	PD (n = 613)	HD (n = 1775)	P
Age, yr	51.0 ± 15.0	55.1 ± 15.3	<0.001
Male, n (%)	309 (50.4)	1004 (56.6)	0.008
Dialysis vintage, mo	19 (9–35)	30 (13–60)	<0.001
Dialysis adequacy, kt/v <sup>b</sup>	2.1 ± 0.5	1.6 ± 0.4	NA
Smoking, n (%)	29 (4.7)	88 (5.0)	0.914
Body mass index, kg/m <sup>2</sup>	22.1 ± 3.2	21.5 ± 3.4	<0.001
Diabetes, n (%)	136 (22.2)	412 (23.2)	0.617
Hypertension, n (%)	566 (92.3)	1447 (81.5)	<0.001
Systolic BP, mmHg	141.6 ± 23.2	143.6 ± 22.0	0.051
Diastolic BP, mmHg	83.1 ± 13.1	83.5 ± 13.1	0.568
Skin autofluorescence, AU	2.8 (2.4–3.4)	2.8 (2.3–3.4)	0.061
CML, μmol/L	52.4 (44.9–58.9)	56.7 (48.8–64.3)	<0.001
Albumin, g/L	39.0 ± 5.5	40.0 ± 6.1	0.009
Hemoglobin, g/L	106.8 ± 20.8	103.5 ± 20.3	<0.001
C-reactive protein, mg/L	3.1 (1.3–8.6)	3.9 (2.1–10.0)	<0.001
Fasting glucose, mM	4.8 (4.3–5.6)	4.9 (4.3–5.6)	0.331
Triglyceride, mM	1.5 (1.1–2.4)	1.3 (1.0–2.0)	<0.001
LDL cholesterol, mM	2.8 ± 0.8	2.3 ± 0.7	<0.001
HDL cholesterol, mM	1.1 ± 0.3	1.1 ± 0.4	0.211
Serum phosphate, mM	2.0 ± 0.5	2.0 ± 0.6	0.182
Serum corrected calcium, mM	2.3 ± 0.2	2.2 ± 0.2	0.170
Cardiovascular morbidity, n (%) <sup>c</sup>	361 (58.9)	1000 (56.3)	0.277
IHD, n (%)	170 (27.7)	373 (21.0)	0.001
HF, n (%)	290 (47.3)	761 (42.9)	<0.001
PVD, n (%)	23 (3.8)	55 (3.1)	0.059
Stroke, n (%)	82 (13.4)	148 (8.3)	0.431

Abbreviation: HD, hemodialysis; PD, peritoneal dialysis; BP, blood pressure; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CML, N<sup>ε</sup>-carboxymethyllysine; NA, not applicable.

<sup>a</sup> Continuous variables were expressed as mean ± SD or median (25th percentile–75th percentile). Categorical variables were expressed as number (percentage).

<sup>b</sup> kt/v was weekly in PD and per session in HD.

<sup>c</sup> Defined as any previous description of ischemic heart disease (IHD), heart failure (HF), stroke or peripheral vascular disease (PVD).

coefficients of variation for autofluorescence measurements were 2.5% and 4.6%, respectively.

Informed consents were obtained from all subjects and appropriate approval was obtained from the local ethics committee.

## 2.5. Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS China, No. db768722083290c38686, Beijing, China). All continuous variables are expressed as mean ± standard deviation (SD) or median

(interquartile range). The continuous data numerical variables were compared with two-sample *t*-test when normally distributed and the Mann–Whitney test when not. Comparisons across multiple groups were performed using one-way ANOVA. Multiple comparisons were conducted with LSD-*t* test when ANOVA was significant. The categorical data were compared with Pearson  $\chi^2$  test. Receiver operating characteristic (ROC) curve for skin autofluorescence to discriminate cardiovascular disease was performed to determine the best cutoff point for skin autofluorescence. Multiple linear enter regression analysis was conducted to determine the relationship of variables with skin autofluorescence. The independent effects of variables on CVD were analyzed by forward stepwise logistic regression analysis ( $P < 0.05$  for entry and  $P \geq 0.10$  for removal). Differences were considered significant at the  $P < 0.05$ .

## 3. Results

### 3.1. Clinical and biochemical characteristics of the patients

A total of 2388 Chinese patients who were enrolled in CCSD were included in this cross-sectional study. Both maintenance PD ( $n = 613$ ) and HD ( $n = 1775$ ) patients were included. Table 1 described the clinical and biochemical characteristics of the patients.

### 3.2. Comparison of skin autofluorescence level between patients on PD and HD

#### 3.2.1. The factors that correlated with skin autofluorescence

Dialysis patients had markedly elevated skin autofluorescence values compared with the age-matched non-CKD reference values. There was no significant difference in the median values of skin autofluorescence between PD and HD patients (Table 1).

To determine the factors that may correlate with skin autofluorescence, a multivariate analysis was conducted in PD and HD patients, separately. As shown in Table 2, age, dialysis duration, diabetes, and cardiovascular morbidity were significantly correlated with skin autofluorescence in both PD and HD patients. In addition, glucose exposure dose used in PD treatment was significantly correlated with skin autofluorescence. In contrast, the concentration of serum CML, a component of AGEs, did not correlate with cardiovascular morbidity, although it correlated with dialysis duration (HD,  $\beta = 0.033$ ,  $P < 0.001$ ; PD,  $\beta = 0.081$ ,  $P < 0.001$ )

**Table 2**  
Factors associated with skin autofluorescence.

	Rs value <sup>a</sup>		$\beta^b$	
	HD (n = 1775)	PD (n = 613)	HD (n = 1775)	PD (n = 613)
Age (yr)	0.433 *	0.493*	0.338*	0.320*
Gender (M = 0, F = 1)	0.059 *	0.016	0.050	−0.013
Smoking (no = 0, yes = 1)	0.020	0.165	0.007	0.007
Body mass index (kg/m <sup>2</sup> )	0.028	0.128*	0.008	−0.026
Dialysis vintage (mo)	0.208*	0.169*	0.204*	0.119*
Diabetes (no = 0, yes = 1)	0.249*	0.390*	0.240*	0.263*
LDL cholesterol (mM)	0.004	0.014	−0.029	0.025
HDL cholesterol (mM)	−0.053	−0.146*	−0.011	0.009
Albumin (g/L)	−0.113*	−0.163*	−0.088	−0.033
Hemoglobin (g/L)	−0.045	−0.059	0.046	0.044
Use of ACE inhibitors/ARBs (no = 0, yes = 1)	−0.054*	−0.025	0.003	−0.043
Glucose exposure dose (g/wk)		0.291*		0.178*
Cardiovascular morbidity (no = 0, yes = 1)	0.125*	0.375*	0.090*	0.161*

Abbreviation: HD, hemodialysis; PD, peritoneal dialysis; skin AF, skin autofluorescence.

<sup>a</sup> Spearman rank correlation test was performed to examine the associations between factors. Rs values are shown \* $P < 0.05$ .

<sup>b</sup> Multiple linear enter regression analyses was performed. The final results were given in the table.  $\beta$  was the standard coefficient; the multiple coefficient of determination ( $R^2$ ) = 0.386 in PD and = 0.215 in HD.

and the level of serum albumin (HD,  $\beta = 0.162$ ,  $P = 0.01$ ; PD,  $\beta = 0.352$ ,  $P < 0.001$ ).

### 3.2.2. Comparison of skin autofluorescence between patients on PD and HD

Because age, dialysis duration, and the presence of diabetes were independently associated with skin autofluorescence in both PD and HD patients, we classified patients by age and dialysis duration in the presence or absence of diabetes. As shown in Fig. 1, skin autofluorescence values were significantly higher in PD compared to HD patients in each category of age and dialysis duration, irrespective of the presence or absence of diabetes ( $P < 0.05$ ).

### 3.3. Relationship between skin autofluorescence and glucose exposure in PD

Complete records of PD solution prescription data were obtained for all 613 PD patients. Patients were classified by their glucose exposure during dialysis. Near 46% (283/613) of the patients had been exposed to lower dose of glucose (760–800 g/wk). Twenty four percent (148/613) of patients had been exposed to moderate dose of glucose (801–1010 g/wk). Only 30% (182/613) patients had been exposed to higher glucose exposure ( $>1010$  g/wk). As shown in Fig. 2, skin autofluorescence values were significantly correlated with averaged glucose dose *per week* (Fig. 2A) and total glucose dose (Fig. 2B) in both diabetic (Fig. 2A<sub>1</sub> & B<sub>1</sub>) and non-diabetic (Fig. 2A<sub>2</sub> & B<sub>2</sub>) PD patients. As shown in Fig. 2C, glucose loading in PD solution increased gradually with prolonged PD duration.

### 3.4. Correlation between skin autofluorescence and cardiovascular morbidity

#### 3.4.1. Cardiovascular morbidity in patients on PD and HD

No significant difference was found in general proportion of CVD when compared PD with HD group. However, significantly more patients on PD had ischemic heart disease and stroke as compared with those on HD (Table 1).

As progression of CVD is a time-dependent process, we analyzed cardiovascular morbidity in patients stratified by age and dialysis duration. As shown in Fig. 3, cardiovascular morbidity increased with age in both PD and HD patients. However, in patients aged 50 years or older, cardiovascular morbidity was significantly more prevalent in those on PD compared to those on HD (Fig. 3A). Similarly, CVD were more prevalent in PD than in HD patients among those who maintained on dialysis for more than 3 years (Fig. 3B).

In our population, the mean age of HD patients was higher than those on PD. Higher mortality in older patients may result in lower cardiovascular morbidity in survivors. However, the annual rate of all-cause mortality in CCSD cohort was 8% in HD and 10% in PD patients, the proportion of cardiovascular death in total mortality was comparable between HD and PD population (52% vs 48%).

#### 3.4.2. The relationship between skin autofluorescence and CVD

There was no significant difference in the median values of skin autofluorescence between patients on PD and HD (Table 3). Patients with skin autofluorescence levels equal and above the median (2.8 AU) had significantly more proportion of CVD compared to those with autofluorescence levels below the median. The higher

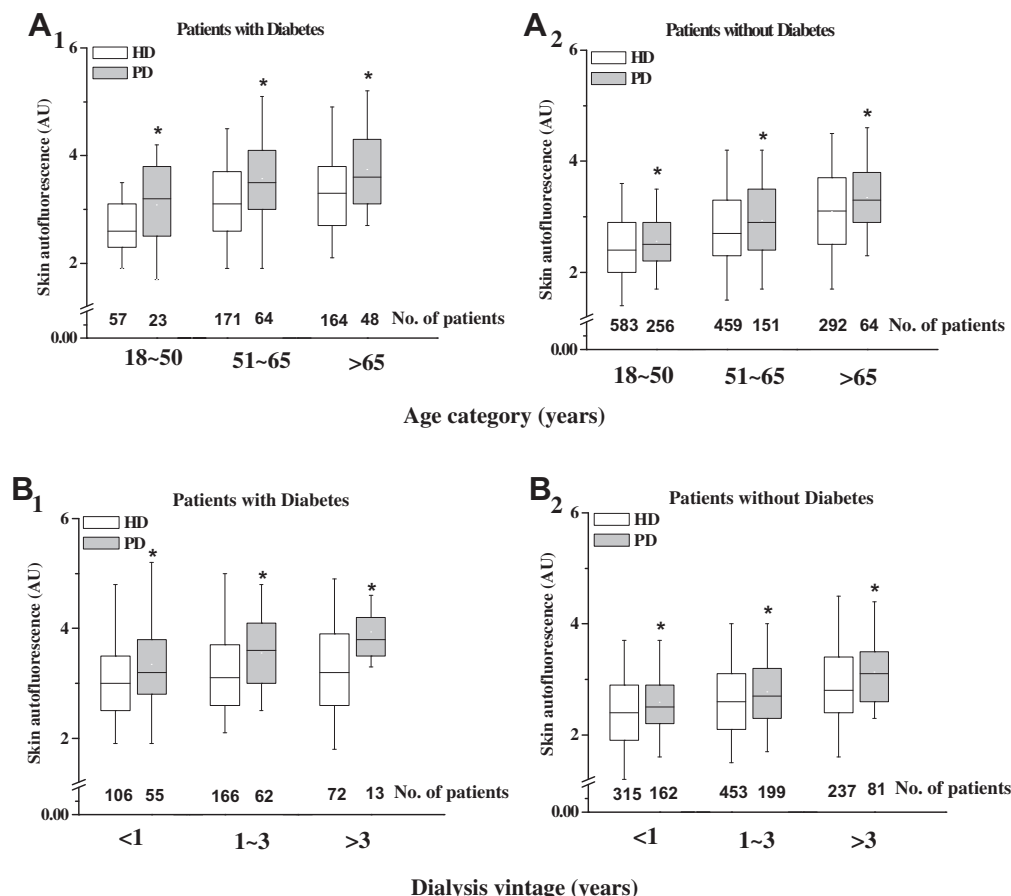
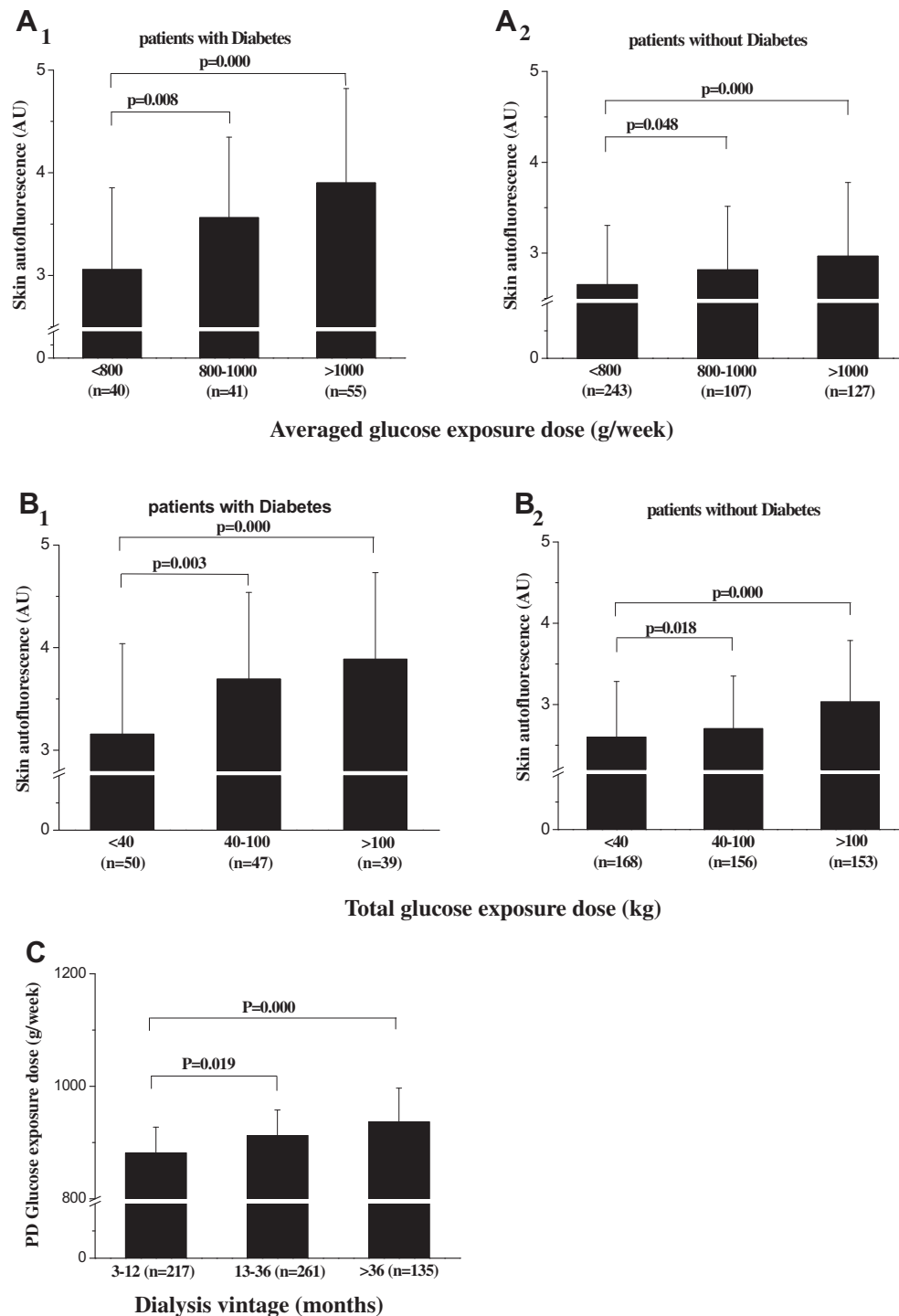


Fig. 1. Comparison of skin autofluorescence levels between PD and HD patients in each category of age (A) and dialysis duration (B) \* $P < 0.05$  vs HD patients.



**Fig. 2.** Relationship between skin autofluorescence and glucose exposure dose in PD patients. A, elevated values of skin autofluorescence were strongly correlated with averaged glucose exposure dose per week in patients with or without diabetes. B, the skin autofluorescence values were correlated with total glucose exposure dose used during PD treatment. C, the average glucose exposure dose during PD increased with dialysis duration. Data were expressed as mean  $\pm$  SD. ANOVA,  $P < 0.001$ .

levels of skin autofluorescence ( $\geq 2.8$  AU) were associated with more proportion of ischemic heart disease, stroke, and heart failure in PD patients (Table 3). To determine the independent effects of skin autofluorescence and other risk factors on cardiovascular morbidity, we performed univariate and multivariate logistic regression analysis using cardiovascular morbidity as the dependent variable. Tables 4 and 5 showed odds ratios for the presence of CVD in HD and PD patients. In addition to traditional risk factors such as old age and hypertension, glucose exposure dose, increased

skin autofluorescence, and increased triglyceride were identified as the independent risk factors for cardiovascular morbidity in PD patients. Glucose exposure dose (OR, 3.313) and skin autofluorescence (OR, 2.854) were still the strongest risk factors for CVD in PD patients after adjustment by age, gender, and the other classic- or uremic-related risk factors.

According to ROC curve, the best cutoff point of skin autofluorescence was determined to be 2.75 (sensitivity 0.585, specificity 0.563, the largest Youden index 0.148).



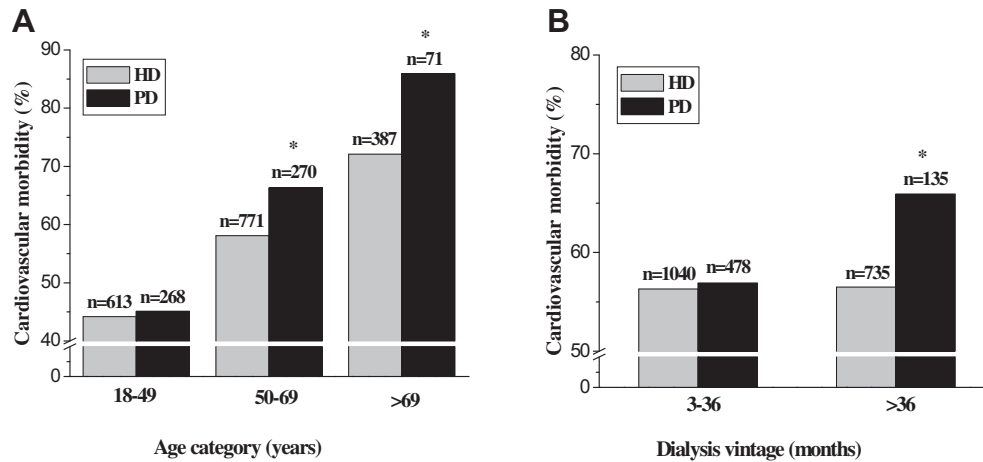


Fig. 3. Comparison of cardiovascular morbidity between PD and HD patients in each category of age (A) and dialysis duration (B) \* $P < 0.05$  in all.

#### 4. Discussion

The main finding of our study is that accumulation of tissue AGEs, measured as skin autofluorescence, was correlated with glucose exposure dose and independently associated with cardiovascular morbidity in ESRD patients undergoing peritoneal dialysis. Patients receiving PD with conventional glucose-containing fluid had significantly higher levels of skin autofluorescence compared to those receiving HD in each category of age and dialysis duration, irrespective of presence or absence of diabetes. Skin autofluorescence values in PD patients strongly correlated with glucose exposure dose. To the best of our knowledge, this is the first study demonstrating that in addition diabetes, high glucose exposure in PD might increase accumulation of tissue AGEs and contribute to cardiovascular morbidity in these patients.

It is known that AGEs are generated in the presence of oxidative stress and additionally accumulate due to decreased renal clearance of AGEs precursors in CKD [8–10]. However, it is not known whether the modality of dialysis, i.e., PD or HD, has additional impact on AGEs accumulation. Consistent with a previous study [23], we observed that skin autofluorescence is increased in ESRD patients receiving either PD or HD and the average values of skin autofluorescence were comparable between PD and HD patients. However, accumulation of tissue AGEs is a time-dependent process, these results could be biased by the difference in age and dialysis duration between patients on the two dialysis modalities. To reduce such a bias, we classified the patients according to the age, dialysis duration, and presence or absence of diabetes. We found that patients receiving PD with glucose-containing fluids had significantly higher levels of skin autofluorescence compared to those receiving HD in each category of age and dialysis duration, irrespective of the presence or absence of diabetes. This is the first

study, with appropriate sample size, that is able to compare skin autofluorescence levels between PD and HD in age- and dialysis duration-matched patients. Because the patients included in the study did not have clinically diagnosed CVD before initiation of dialysis, it is likely that PD process using conventional glucose-containing solutions may lead to additional increase in risk for CVD.

A main difference exists between patients on PD and HD—the peritoneal cavities of PD patients are exposed to a dialysis solution. The PD patients enrolled in the study were all treated by the conventional PD solution which contained high concentration of glucose and GDPs [22,29]. Both glucose and GDPs exposure have been implicated in the development of AGEs in those receiving PD [30,31]. We demonstrated in this study that skin autofluorescence elevated with increasing duration of PD and significantly correlated with glucose exposure dose in patients receiving PD, suggesting that cutaneous AGEs levels may reflect long-term metabolic burden in PD patients. A recent work by the Euro Balance group also shows that markers of AGEs generation reflect the composition of PD solution [32]. Since glucose loading in PD solution increasing with PD duration, it is possible that long-term exposure to high concentration of dialyzate glucose or GDPs may damage the peritoneum and lead to decrease in peritoneal ultrafiltration [6,33]. It may, in turn, increase the requirement of osmotic glucose, and further increase the metabolic burden. New PD solutions which contain an alternative osmotic agent such as icodextrin or amino acid have been developed. Using of PD solution that is low in GDPs results in prolonged technique survival, and, more importantly, also patient survival [32,34–37].

The relationship between tissue AGEs and CVD in PD patients has not been well established. Our study found that CVD was significantly more prevalent in those with higher ( $\geq$ median) than those with lower ( $<$ median) skin autofluorescence values in both

**Table 3**  
Cardiovascular morbidity in dialysis patients classified by the median<sup>a</sup> of skin autofluorescence.

	PD (n = 613)			HD (n = 1775)		
	Skin AF $\geq$ 2.8	Skin AF $<$ 2.8	P	Skin AF $\geq$ 2.8	Skin AF $<$ 2.8	P
Cardiovascular morbidity, n (%)	243 (72.3)	118 (42.6)	$<0.001$	553 (60.8)	447 (51.6)	$<0.001$
IHD, n (%)	121 (36.0)	49 (17.7)	$<0.001$	223 (24.5)	150 (17.3)	$<0.001$
HF, n (%)	198 (58.9)	92 (33.2)	$<0.001$	410 (45.1)	351 (40.5)	0.055
Stroke, n (%)	64 (19.0)	18 (6.5)	$<0.001$	84 (9.2)	64 (7.4)	0.170
PVD, n (%)	17 (5.1)	6 (2.2)	0.086	31 (3.4)	24 (2.8)	0.494

Abbreviation: HD, hemodialysis; PD, peritoneal dialysis; skin AF, skin autofluorescence; IHD, ischemic heart disease; HF, heart failure; PVD, peripheral vascular disease.

<sup>a</sup> The median of skin AF was 2.8 AU in both PD and HD patients.

**Table 4**Variables related to cardiovascular disease in HD patients by logistic regression analysis<sup>a</sup>.

variables	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age $\geq$ 50 yr (no = 0, yes = 1)	2.129	1.745–2.590	0.000	2.175	1.628–2.906	0.000
Gender (M = 1, F = 2)	1.094	0.905–1.322	0.352	–	–	–
Smoking (no = 0, yes = 1)	2.419	1.479–3.956	0.000	1.916	1.072–3.422	0.028
BMI $\geq$ 24 kg/m <sup>2</sup> (no = 0, yes = 1)	1.107	0.881–1.391	0.382	–	–	–
Diabetes (no = 0, yes = 1)	2.319	1.827–2.943	0.000	1.443	1.040–2.002	0.028
Hypertension (no = 0, yes = 1)	1.823	1.431–2.321	0.000	2.123	1.513–2.980	0.000
Skin autofluorescence (AU)	1.344	1.197–1.485	0.000	1.239	1.056–1.453	0.008
CML ( $\mu$ mol/L)	1.006	0.998–1.013	0.163	–	–	–
Triglyceride $>$ 1.7 mM (no = 0, yes = 1)	1.024	0.821–1.278	0.830	–	–	–
LDL cholesterol $>$ 3.36 mM (no = 0, yes = 1)	1.497	0.989–2.266	0.057	–	–	–
HDL cholesterol $<$ 0.92 mM (no = 0, yes = 1)	0.968	0.762–1.231	0.793	–	–	–
Albumin $\leq$ 3.5 g/L (no = 0, yes = 1)	1.176	0.933–1.482	0.171	–	–	–
Hemoglobin $\leq$ 90 g/L (no = 0, yes = 1)	1.604	1.282–0.006	0.000	1.467	1.079–1.993	0.014
C-reactive protein $>$ 3 mg/L (no = 0, yes = 1)	1.442	1.128–1.844	0.004	–	–	–
Fasting glucose $>$ 7.0 mM (no = 0, yes = 1)	1.024	0.821–1.278	0.830	–	–	–
Dialysis vintage $>$ 3 yr (no = 0, yes = 1)	1.009	0.834–1.220	0.929	–	–	–

Abbreviation: HD, hemodialysis; OR, odds ratio; CI, confidence interval; BMI, body mass index.

<sup>a</sup> The independent effects of variables on CVD were analyzed by forward stepwise logistic regression analysis ( $P < 0.05$  for entry and  $P \geq 0.10$  for removal).**Table 5**Variables related to cardiovascular disease in PD patients by logistic regression analysis<sup>a</sup>.

variables	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age $\geq$ 50 yr (no = 0, yes = 1)	2.129	1.745–2.597	0.000	1.607	1.060–2.436	0.026
Gender (M = 1, F = 2)	0.999	0.724–1.379	0.996	–	–	–
Smoking (no = 0, yes = 1)	2.271	0.955–5.401	0.063	–	–	–
BMI $\geq$ 24 kg/m <sup>2</sup> (no = 0, yes = 1)	1.519	1.040–2.220	0.031	–	–	–
Diabetes (no = 0, yes = 1)	2.782	1.800–4.299	0.000	–	–	–
Hypertension (no = 0, yes = 1)	2.478	1.344–4.569	0.004	2.336	1.104–4.939	0.026
Skin autofluorescence (AU)	3.206	2.459–4.179	0.000	2.854	2.062–3.950	0.000
CML ( $\mu$ mol/L)	1.001	0.985–1.018	0.890	–	–	–
Triglyceride $>$ 1.7 mM (no = 0, yes = 1)	1.848	1.314–2.600	0.000	1.539	1.024–2.314	0.038
LDL cholesterol $>$ 3.36 mM (no = 0, yes = 1)	0.682	0.458–1.018	0.061	–	–	–
HDL cholesterol $<$ 0.92 mM (no = 0, yes = 1)	1.346	0.921–1.968	0.125	–	–	–
Albumin $\leq$ 3.5 g/L (no = 0, yes = 1)	2.179	1.414–3.358	0.000	1.761	1.014–3.060	0.045
Hemoglobin $\leq$ 90 g/L (no = 0, yes = 1)	0.820	0.547–1.230	0.338	–	–	–
C-reactive protein $>$ 3 mg/L (no = 0, yes = 1)	1.697	1.194–2.413	0.003	–	–	–
Fasting glucose $>$ 7.0 mM (no = 0, yes = 1)	4.194	2.205–7.977	0.000	2.241	1.116–4.499	0.023
Glucose exposure dose (g/w)	5.340	2.795–10.201	0.000	3.313	1.514–7.248	0.003
Dialysis vintage $>$ 3 yr (no = 0, yes = 1)	1.465	0.983–2.184	0.061	–	–	–

Abbreviation: PD, peritoneal dialysis; OR, odds ratio; CI, confidence interval; BMI, body mass index.

<sup>a</sup> The independent effects of variables on CVD were analyzed by forward stepwise logistic regression analysis ( $P < 0.05$  for entry and  $P \geq 0.10$  for removal).

dialysis modalities. The power of skin autofluorescence, as an independent risk factor for CVD in PD patients, is illustrated by the fact that glucose exposure dose and skin autofluorescence were found to serve best in the multiple logistic regression model than the other known risk factors, suggesting an independent relationship between skin autofluorescence and CVD in chronic PD patients.

Accumulation of AGEs might be an additional important factor in the development or worsening of structural and functional changes within vasculature. AGEs deposit in the vessel wall and contribute to the progression of CVD by several mechanisms, including cross-linking of proteins, binding to the receptor for inducing oxidative stress, inflammation, and endothelial dysfunction [5,35,37–39]. Indeed, the close relationship between accumulation of tissue AGEs and cardiovascular mortality has been demonstrated in patients with diabetes [13,17].

In conclusion, our study showed that cutaneous AGEs levels measured by skin autofluorescence were significantly higher in PD than in HD patients in each category of age and dialysis duration, irrespective of the presence or absence of diabetes. Skin autofluorescence was the strongest independent risk factor for CVD in

patients on maintenance PD. As skin autofluorescence correlated to glucose exposure dose and PD duration, our study provides a previously unappreciated link between PD exposure of metabolic stress and progression of cardiovascular disease in patients on long-term PD. The close relationship between tissue AGEs accumulation and CVD morbidity in PD patients warrants interventions specifically aimed at AGEs accumulation in this population.

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