Int Urol Nephrol (2014) 46:817–824
DOI 10.1007/s11255-013-0597-6

NEPHROLOGY - ORIGINAL PAPER

Advanced glycation end products, aortic stiffness, and wave reflection in peritoneal dialysis as compared to hemodialysis

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Received: 15 July 2013 / Accepted: 25 October 2013 / Published online: 17 November 2013

Abstract
Background Modification of vascular extracellular matrix by advanced glycation end products (AGEs) may result in vascular stiffness. Because of higher exposure to glucose, we hypothesized that patients on peritoneal dialysis (PD) may have higher tissue levels of AGEs, increased vascular stiffness, and enhanced central augmentation pressure as compared to hemodialysis patients (HD).
Methods In a cross-sectional study, 43 PD were matched to 43 HD based on age, gender, diabetes, and dialysis vintage. Tissue levels of AGEs were assessed by skin autofluorescence (skin AF). Aortic stiffness was measured by carotid-femoral pulse wave velocity (cf-PWV), and heart rate-adjusted augmentation pressure (AP@75) was performed by arterial tonometry.
Results Baseline characteristics were similar in both groups except for lower prevalence of cardiovascular disease (CVD) and higher exposure to smoking in PD. Skin AF and cf-PWV were not statistically different, but PD patients had a lower AP@75 ($P = 0.023$). However, after adjustments for prevalence of CVD and smoking status, skin AF was higher in PD by 0.587 AU (95 % CI 0.091–1.215, $P = 0.020$), and cf-PWV was higher in PD by 2.20 m/s (95 % CI 0.56–3.84, $P = 0.009$), while AP@75 was not different. Overall, there was a significant association between skin AF and cf-PWV and AP@75.
Conclusion Skin AF and aortic stiffness were higher in PD after adjustments for imbalances in baseline characteristics. Independent of dialysis modality, there was a positive association between skin AF, aortic stiffness, and enhanced wave reflection.

Keywords Chronic kidney disease · Dialysis · Advanced glycation end products · Skin autofluorescence · Aortic stiffness · Augmentation pressure

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Introduction

The high prevalence of cardiovascular disease (CVD) among patients with advanced chronic kidney disease (CKD) cannot be explained solely by traditional cardiovascular risk factors. Recently, aortic stiffness and enhanced wave reflection, which result in increased central pulse pressure (PP), cardiac workload, and left ventricular hypertrophy, have been shown to be an independent predictor for cardiovascular morbidity and mortality in CKD [1–4]. The mechanisms of aortic stiffness are complex and poorly understood. However, advanced glycation end products (AGEs) maybe involved in the pathophysiology of vascular disease in CKD. Indeed, AGEs can crosslink proteins of extracellular matrix (collagen and elastin), altering their physical properties, which translates into increased aortic stiffness [5–7].

In order to assess the tissue content of AGEs noninvasively, determination of skin autofluorescence (skin AF) has been developed as a surrogate marker of AGEs-modified structural proteins. Skin AF has an excellent

correlation with both fluorescent and nonfluorescent AGEs extracted from skin biopsies [8]. Some studies have now shown the relationship between skin AF and cardiovascular risk factors, CVD, and mortality [9–14].

In addition to uremia, renal replacement by peritoneal dialysis (PD) exposes patients to high glucose concentrations and glucose degradation products (GDP), which occurs in the process of PD solution heat sterilization, accelerating formation of AGEs in the peritoneal cavity. GDP and AGEs can cause mesothelial damage and increase peritoneal vascularization and fibrosis that ultimately lead to ultrafiltration failure [15]. Exposure to glucose may result in increased serum and tissue AGEs after initiation of PD, and is shown to be associated with increased skin AF and CVD [16–18].

In light of the potential role of AGEs in vascular disease and exposure to PD fluids, we hypothesized that AGEs, aortic stiffness, and central augmentation pressure are enhanced in PD patients as compared to HD patients. Therefore, the present study aims to evaluate aortic stiffness, central hemodynamic parameters of blood pressure, and its relation to skin AF in a group of PD patients matched to hemodialysis (HD) patients.

Methods

Study design and population

This is a cross-sectional study that evaluated tissue AGEs, aortic stiffness, and central augmentation pressure in PD patients as compared to HD. The study was conducted at CHU de Québec-L'Hôtel-Dieu de Québec Hospital between 2007 and 2010. Eligibility criteria for the study included age >18 years, chronic PD, or HD (>3 months) with stable dry weight. Patients were excluded if they had any clinical conditions that would hamper hemodynamic measurements (absence of femoral pulse, systolic blood pressure of <90 mmHg) or acute episode of illness (infection, acute heart failure, active bleeding). Forty-three of the 50 eligible PD patients were matched to 43 of the 204 eligible HD patients. The patients were matched based on decade of age, gender, status of diabetes, and duration of dialysis (<1 year, 1–3, >3 years). Baseline medical history, laboratory data, and pharmacological treatment were recorded. CVD was defined by a history of stroke, coronary artery disease, lower extremity amputation, or revascularization. Coronary artery disease was defined as myocardial infarction, coronary artery revascularization, or ischemic heart disease as shown by either a treadmill, echo, or thallium stress tests. The study was approved by the institution review board, and all patients provided informed consent.

Dialysis parameters

Patients on PD were on manual exchange ($n = 17$) or automated nocturnal PD ($n = 26$), using a combination of glucose-based regimen (Dianeal, Baxter Healthcare) with or without 7.5 % icodextrin (Extraneal, Baxter Healthcare). Hemodialysis was performed 3 times weekly with dialysis duration of 3–4 h, a blood flow of 350–400 mL/min, and a dialysate flow of 500–750 mL/min. A bicarbonate-based buffer dialysis solution was used with sodium concentrations of 136 to 142 mmol/L and calcium concentrations of 1.25 or 1.5 mmol/L. The dialysis membranes were mainly composed of polysulfone or triacetate cellulose with a surface area of between 1.7 and 2.1 m^2.

Hemodynamic measurements

Hemodynamic measurements were performed after 15 min of rest in a supine position prior to the mid-week dialysis session in HD patients. In case of an arteriovenous fistula, measurements were performed on the contralateral arm. In PD patients, a validation study ($n = 20$) was first performed to examine whether the presence of dialysis fluid in the peritoneal cavity could alter aortic stiffness and pulse wave reflection, where we found no significant difference in carotid-femoral pulse wave velocity (cf-PWV) without dialysis fluid 12.7 ± 4.0 versus with dialysis fluid 12.7 ± 3.7, respectively ($P = 0.96$). Therefore, in PD patients, hemodynamic measurements were performed either with or without dialysis solution in the peritoneal cavity. Brachial artery blood pressure (BP) was recorded using the oscillometric automatic sphygmomanometer BPM-100 (BP-Tru, Coquitlam, Canada). BP was recorded 6 times, with a 2-min interval between each measurement, and the average of the last 5 measurements was used to determine the brachial systolic and diastolic BP [19]. We determined cf-PWV using Complior® SP system (Artech Medical, Pantin, France) as described previously [20, 21]. Briefly, the sensors were positioned over carotid, and femoral arteries and the transit times were determined. Three consecutive recordings were performed to determine the transit time by the maximal upstroke algorithm, followed by measurement of direct distance between the two probes. For the purpose of comparison to the reference values published, standard cf-PWV was obtained taking into account differences in the transit time using the maximal upstroke algorithm, and the overestimation of true distance by multiplying direct distance by 0.8 [22]. An abnormal cf-PWV is defined as a standard cf-PWV that is superior to the decade-specific 90th percentile of normal subjects [22]. To assess the impact of aortic stiffness on central pulse wave profile, radial pulse wave profile was recorded by aplanation tonometry after recalibration with

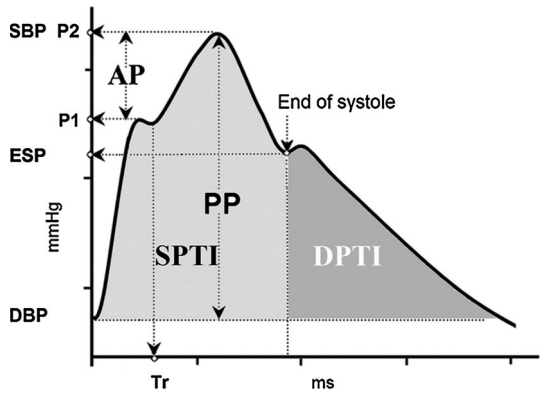

Fig. 1 Central pulse wave profile. The components of central pulse wave profile are as follows: first peak of pressure (*P1*), second peak of pressure (*P2*), end-systolic pressure (*ESP*), time of return of the reflection wave (*Tr*), diastolic blood pressure (*DBP*), systolic blood pressure (*SBP*), pulse pressure (*PP*), systolic pressure time index (*SPTI*), diastolic pressure time index (*DPTI*), and augmentation pressure (*AP*)

systolic and diastolic brachial BP (SphygmoCor system®, AtCor Medical Pty. Ltd., Sydney, Australia). Three consecutive recordings were performed, and central pulse wave profile was constructed using the generalized transfer function as previously described and validated [21, 23]. Central systolic BP (SBP), diastolic BP (DBP), mean BP (MBP), pulse pressure (PP), time of return of the reflected wave (Tr), central augmented pressure (AP) and heart rate adjusted AP (AP@75), and central augmentation index (AIx) (AIx = (AP/PP) × 100) were evaluated. Figure 1 illustrates the components of central pulse wave analysis.

Laboratory data

Basic laboratory data in relation to anemia, nutrition, mineral metabolism, and highly sensitive C-reactive protein (hsCRP) were collected from the patient records using the average or the median of the available data from the previous 3 months prior to the evaluation. The determination of parathyroid hormone (PTH) was performed using PTH stat assay from Roche diagnostics using two antibodies reactive with epitopes in the amino acid regions 26–32 and 37–42. The samples were stored at −80 °C until assayed for specific biomarkers. Pentosidine was measured by high-performance liquid chromatography assay as described previously [21]. Skin AF was determined using the AGE-Reader™ (DiagnOptics Technologies BV). AGE-Reader illuminates a skin surface of 4 cm^2 guarded against surrounding light with an excitation light source (peak $\lambda_{exc} = 370$ nm). Emission light (fluorescence with $\lambda = 420$–600 nm) and reflected excitation light (with $\lambda = 300$–420 nm) from the skin are measured with a spectrometer. Skin AF is calculated as follows: (emission light/reflected excitation light) × 100 (in arbitrary units).

Data analysis

Results are expressed as mean ± SD or median (25th–75th percentile). Chi-square, Student's *T* test, or Mann–Whitney *U* test were used to compare data variable between two groups where appropriate. Data that did not follow a normal distribution were log-transformed. Multivariable regression analysis was performed to construct models adjusted for biological related confounders that were different between groups (CVD, smoking status, BMI, albumin, residual renal function, and pentosidine levels). The impact of skin AF on aortic stiffness and wave reflection was examined by a multivariable analysis taking into account known determinants of aortic stiffness and wave reflection. To examine the relationship between skin AF and cf-PWV, we looked at unadjusted relationships and then adjusted for MBP (as cf-PWV is highly dependent on MBP). As age is both a strong determinant of skin AF and aortic stiffness, we examined whether age was a confounder by introducing the age into the equation, and indeed, introduction of age into the model reduced the extent of the relationship between cf-PWV and skin AF. Since the results were negative after incorporation of age into the model, further analyses were not performed. The same approach was used for AP. As AP is influenced biologically by mean blood pressure, gender, and age, we performed sequential adjustments. Since the effect of interest was the relationship between skin AF and AP, and skin AF and both age and diabetes are known strong determinants of skin AF, we decided to adjust for these two variables. Finally, because AP can be influenced by cf-PWV, and cf-PWV can potentially be associated with skin AF, we incorporated cf-PWV into the multivariable adjusted model to examine whether this association would disappear upon incorporation of cf-PWV. We further explored the impact of dialysis modality on skin AF after stratification by diabetes status with interaction terms generated to evaluate for effect modification. Data analysis was performed using SPSS software version 19.0 for Windows. A two-tailed *P* value of <0.05 was considered to be statistically significant.

Results

Patient population

The groups were comparable in terms of age, gender distribution, status of diabetes, and duration of dialysis by design (Table 1). However, PD patients had less CVD, greater exposure to smoking, higher body mass index (BMI) and waist circumference, lower levels of albumin, and a better residual renal function (Table 1). The brachial

Table 1 Baseline clinical and biochemical characteristics of subjects

	PD ($n = 43$)	HD ($n = 43$)	P value
Age (year)	62 ± 13	63 ± 14	0.902
Male [n (%)]	25 (58 %)	25 (58 %)	1.000
Weight (kg)	80 ± 18	71 ± 18	**0.016**
Height (cm)	167 ± 9	165 ± 11	0.209
BMI (kg/m^2)	29 ± 6	26 ± 5	**0.032**
Waist (cm)	106 ± 15	95 ± 15	**0.005**
Hips (cm)	107 ± 10	101 ± 12	**0.032**
Diabetes [n (%)]	14 (33 %)	14 (33 %)	1.000
Cardiovascular disease [n (%)]	5 (12 %)	27 (63 %)	**<0.001**
Current/past smoking [n (%)]	27 (63 %)	13 (30 %)	**0.005**
Dialysis vintage (months)	72 (33–151)	63 (38–123)	0.907
Dialysis Kt/v[a]	1.5 ± 0.26	1.7 ± 0.3	–
Daily renal Kt/v	0.04 (0.01–0.09)	0 (0–0)	**<0.001**
Laboratory			
Hb (g/L)	117 ± 13	118 ± 14	0.827
HbA1c (%)[b]	0.061 ± 0.008	0.059 ± 0.007	0.451
Urea (mmol/L)	21.9 ± 6.6	20.3 ± 6.0	0.274
Creatinine (μmol/L)	889 ± 283	816 ± 221	0.189
Ca (mmol/L)	2.23 ± 0.28	2.24 ± 0.17	0.898
Albumin (g/L)	37 ± 4	39 ± 3	**0.019**
P (mmol/L)	1.64 ± 0.53	1.63 ± 0.44	0.848
PTH (ng/L)	342 (179-510)	336 (223-638)	0.398
hsCRP (mg/L)	5.0 (2.0–11.5)	5.3 (2.5–10.2)	0.946
Ferritine	503 (328–690)	314 (121–457)	**<0.001**
Iron sat (%)	27.9 ± 10.7	25.0 ± 10.2	0.205
Transferrine (g/L)	2.02 ± 0.39	1.76 ± 0.32	**0.001**
Total cholesterol (mmol/L)	4.50 ± 1.25	3.58 ± 0.87	**<0.001**
TG (mmol/L)	2.70 ± 1.78	1.79 ± 1.00	**0.004**
HDL (mmol/L)	0.89 (0.77–1.20)	0.97 (0.79–1.22)	0.580
LDL (mmol/L)	2.52 ± 1.00	1.75 ± 0.67	**<0.001**
Medication			
ASA [n (%)]	30 (70 %)	23 (54 %)	0.123
Plavix [n (%)]	5 (12 %)	8 (19 %)	0.369
Statins [n (%)]	36 (84 %)	28 (65 %)	**0.049**
ACEi [n (%)]	7 (16 %)	7 (16 %)	1.000
ARB [n (%)]	9 (21 %)	11 (26 %)	0.612
CCB [n (%)]	13 (30 %)	13 (30 %)	1.000
Beta-blocker [n (%)]	25 (58 %)	26 (61 %)	0.827
Diuretics [n (%)]	19 (44 %)	7 (16 %)	**0.005**
ESA [n (%)]	35 (81 %)	38 (88 %)	0.369
Calcium (mg/day)	1,279 ± 1,098	1,011 ± 612	0.167
Sevelamer [n (%)]	13 (30 %)	25 (58 %)	**0.01**
1(OH)-VitD_3 (μg/week)	0.75 (0.00–2.25)	0.50 (0.00–1.50)	0.075

Results are means ± SD, n (%), or median (IQR)

Statistically significant differences are highlighted in bold

ACEi ACE inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blockers, *ESA* erythropoietin stimulating agents

[a] Kt/v is weekly in PD and per session in HD

[b] Only in diabetic patients

Table 2 Hemodynamic and study parameters

	PD	HD	P value
HR	66 ± 10	68 ± 8	0.456
Brachial (mmHg)			
SBP	126 ± 26	130 ± 27	0.511
DBP	76 ± 10	70 ± 13	**0.042**
PP	51 ± 24	60 ± 22	**0.027**
Central			
SBP (mmHg)	118 ± 25	121 ± 26	0.570
DBP (mmHg)	77 ± 10	71 ± 13	**0.044**
MBP (mmHg)	93 ± 14	91 ± 17	0.576
PP (mmHg)	41 ± 23	50 ± 21	**0.022**
P1 (mmHg)	104 ± 16	104 ± 19	0.942
T1 (ms)	105 ± 13	106 ± 11	0.847
P2 (mmHg)	117 ± 25	121 ± 26	0.570
T2 (ms)	222 ± 27	228 ± 20	0.223
AP@75 bpm (mmHg)	10.4 ± 7.3	13.6 ± 7.3	**0.023**
Aix@75 bpm (%)	25 ± 10	28 ± 7	0.209
TR (ms)	137 ± 15	137 ± 12	0.948
SPTI (mmHg ms)	2,230 ± 460	2,377 ± 530	0.176
DPTI (mmHg ms)	3,359 ± 502	3,098 ± 637	**0.040**
SEVR (%)	155 ± 28	134 ± 30	**0.002**
cf-PWV (m/s)	13.22 ± 3.37	12.46 ± 3.82	0.345
Standard cf-PWV (m/s)	12.41 ± 3.66	11.56 ± 4.14	0.345
Abnormal cf-PWV [n (%)]	20 (47 %)	23 (53 %)	0.518
Pentosidine (pmol/mL)	258 (165–436)	467 (323–553)	**<0.001**
Skin AF	2.99 ± 0.85	2.97 ± 0.96	0.935

Results are means ± SD or n (%)

Statistically significant differences are highlighted in bold

AP augmentation pressure, *AIx* augmentation index adjusted for a heart rate of 75 beats per minute, *Tr* time of wave return, *DPTI* diastolic pressure time index, *SPTI* systolic pressure time index, *cr-PWV* carotid-radial pulse wave velocity, *cf-PWV* carotid-femoral pulse wave velocity. Standard cf-PWV refers to adjustments performed for the maximal upstroke algorithm and direct distance measurement; abnormal cf-PWV defined as the standard cf-PWV that is higher than the decade-specific 90th percentile of normal subjects

Table 3 Impact of peritoneal dialysis on skin AF

Predictors	Slope	95 % CI	*P* value
Unadjusted	0.018	−0.399 to 0.435	0.934
Adjusted			
Model 1	0.587	0.091 to 1.084	**0.020**
Model 2	0.637	0.107 to 1.168	**0.019**
Model 3	0.788	0.169 to 1.407	**0.013**

Statistically significant differences are highlighted in bold

Model 1: adjusted for cardiovascular disease and smoking

Model 2: adjusted for parameters in Model 1 + body mass index and albumin

Model 3: adjusted for parameters in Model 2 + pentosidine (log) and residual renal function

Table 4 Impact of dialysis modality on skin AF as stratified by diabetes status

Diabetes status	Dialysis modality	Skin AF (95 % CI)
No ($n = 58$)	PD ($n = 29$)	2.97 (2.66–3.29)
	HD ($n = 29$)	2.95 (2.44–3.45)
Yes ($n = 28$)	PD ($n = 14$)	3.02 (2.41–3.62)
	HD ($n = 14$)	3.01 (2.57–3.45)

and estimated central blood pressures and pulse wave analysis data are provided in Table 2. The brachial and central diastolic blood pressures were higher in PD patients, while brachial and central PPs were lower.

Impact of peritoneal dialysis on skin AF, aortic stiffness, and wave reflection

Skin AF was not statistically different with regard to dialysis modality (Table 1). However, Table 3 shows that after adjustments for prevalence of CVD and smoking status, PD patients had a higher degree of skin AF (Model 1). The higher levels of skin AF still remained significant after incorporation of albumin and BMI (Model 2), and subsequently by adding pentosidine and residual renal function into the model (Model 3).

Stratification by diabetes status showed no significant impact of dialysis modality on skin AF (Table 4). There was no significant interaction between dialysis modality and diabetes in unadjusted ($P = 0.996$) and adjusted models incorporating CVD and smoking status ($P = 0.856$).

There were no statistically significant difference in cf-PWV before or after adjustments for mean blood pressure (0.55 m/s, 95 % CI −0.86 to 1.96, $P = 0.444$). However, after adjustments for CVD and smoking status, PD patients had a higher cf-PWV (2.20 m/s, 95 % CI 0.56–3.84, $P = 0.009$). Upon further adjustments for BMI and albumin, cf-PWV was not significantly higher in PD patients (1.08 m/s, 95 % CI −0.64 to 2.80, $P = 0.218$).

Table 5 The relationship between skin AF and cf-PWV

Dependant variable	Predictors	Slope	95 % CI	*P* value
cf-PWV (m/s)	*Skin AF (AU)*			
	Unadjusted	1.092	0.149–2.034	**0.023**
	Adjusted			
	Model 1	0.843	0.008–1.679	**0.048**
	Model 2	0.119	−0.436 to 0.674	0.675

Statistically significant differences are highlighted in bold

Model 1: adjusted for mean blood pressure

Model 2: adjusted for mean blood pressure and age

Table 6 The relationship between skin AF and augmentation pressure

Dependant variable	Predictors	Slope	95 % CI	*P* value
AP@75 (mmHg)	*Skin AF (AU)*			
	Unadjusted	3.17	1.47–4.87	**<0.001**
	Adjusted			
	Model 1	2.51	1.04–3.98	**0.001**
	Model 2	1.57	0.36–2.78	**0.011**
	Model 3	1.63	0.40–2.85	**0.009**
	Model 4	1.56	0.38–2.73	**0.009**

AP@75: augmentation pressure adjusted for heart rate of 75 beats per minute

Statistically significant differences are highlighted in bold

Model 1: adjusted for mean blood pressure, gender

Model 2: adjusted for parameters in Model 1 + age

Model 3: adjusted for parameters in Model 2 + diabetes

Model 4: adjusted for parameters in Model 3 + cf-PWV

In the model adjusted for MBP, CVD, and smoking, incorporation of skin AF showed that higher cf-PWV in PD patients were not statistically significant (1.724 m/s, 95 % CI −0.19 to 3.64, $P = 0.078$).

The timing of wave reflection was not different. However, AP@75 was lower in PD patients, and the diastolic pressure time index was higher, resulting in a better subendocardial viability ratio. After correction for mean blood pressure, PD patients had a lower AP@75 by −3.7 mmHg (95 % CI 1.1–6.4, $P = 0.005$). However, after adjustments for mean blood pressure, CVD, and smoking status, this difference was reduced to 1.4 mmHg and was no longer statistically significant (95 % CI −2.0 to 4.7 mmHg, $P = 0.413$).

Impact of skin AF on aortic stiffness and wave reflection

There was a statistically significant association between skin AF and cf-PWV before (Table 5, unadjusted) and after

adjustment for mean blood pressure (Table 5, Model 1). In these models, dialysis modality had no impact on the relationship between skin AF and cf-PWV. However, upon incorporation of age into the model, the relationship between skin AF and cf-PWV was no longer significant (Model 2 of Table 5).

There was a statistically significant association between skin AF and central AP@75 (Table 6). After adjustment for known determinants of AP, such as mean blood pressure and gender (Table 6, Model 1), other clinical conditions, and cf-PWV (Table 6, Models 2–4), there was still a statistically significant association between skin AF and AP@75.

Through univariate and multivariate analysis, we also explored but found no impact of statins or angiotensin converting enzyme inhibitor/angiotensin receptor blocker on skin AF, cf-PWV, or AP@75.

Discussion

This study shows that skin AF and aortic stiffness were higher in PD patients after adjustments for imbalances in baseline characteristics. Skin AF was positively associated with aortic stiffness, but this association disappeared after adjustment for age. However, skin AF was associated with higher augmentation pressure, in both unadjusted and adjusted models.

It has long been established that serum AGEs reach higher levels in CKD and that contrary to diabetes, the level of AGEs are independent of glycemic control. In CKD, accumulation of AGEs is thought to be caused by the retention of food-derived AGEs and by accumulation of reactive carbonyl compounds through both oxidative and non-oxidative pathways [24, 25]. As most of circulating AGEs are protein-bound, their total removal by dialysis is limited in reducing systemic levels of AGEs and even more so in HD patients [26]. Skin AF is a noninvasive method of assessing the extent of modification of proteins by AGEs. Studies have now reported the relationship between skin AF and CVD and mortality in CKD patients [9, 13, 18, 27, 28]. Indeed, AGEs are a heterogeneous group of molecules, and it may be difficult to establish an association between a specific serum AGE level and the degree of the modification of proteins by an ensemble of AGEs as determined by skin AF. This is in agreement with the observation that not only fluorescent AGEs, namely pentosidine, but also nonfluorescent AGEs such as carboxymethyllysine and *N*-carboxyethyl-lysine in skin biopsies are shown to be strongly associated with skin AF [8]. These observations can only underline the heterogeneity in physical, biochemical, and biological activities of AGEs.

Only few studies have looked at AGEs accumulation depending on the dialysis modality [17, 18, 29]. In a large cross-sectional study, Jiang et al. [18] also showed a higher level of skin AF in PD patients that was related to dialysis vintage and glucose exposure. They also showed that higher glucose exposure and skin AF were strong risk factors for cardiovascular morbidity in PD patients even after adjustment for other classic or uremic risk factors. In a smaller study (53 PD patients, 62 HD patients), keeping in mind that the PD patients had a shorter dialysis vintage, McIntyre and colleagues [17] failed to show a difference in skin AF. Nevertheless, they showed that skin AF correlated with age in both groups but with dialysis vintage only in PD patients. In another study (102 PD patients, 157 HD patients), Oleniuc and colleagues [29] found that PD patients had lower skin AF ($P = 0.09$). However, these findings could be explained by a shorter dialysis vintage, a younger age, and a better residual renal function. In our study, we matched patients in order to have comparable groups in terms of age, gender, dialysis vintage, and diabetes. Despite matching for these parameters, our PD patients had a lower prevalence of CVD, higher smoking exposure, BMI and pentosidine, and a better residual renal function. We therefore constructed various models in order to adjust for these important baseline imbalances between groups and showed that PD patients had a higher level of skin AF as compared to HD patients. Confounding is a major concern in observational studies because it results in biased estimation of exposure effects. In the extreme, this can mean that a true effect is hidden. Therefore, statistical corrections that produce "adjusted" estimates of the exposure effect are needed to unmask an association not present in the unadjusted analyses, as was seen in this study for the relationship of dialysis modality with AGEs.

Aortic stiffness, a principal determinant of increased PP, is associated with increased risk of CVD and mortality in CKD patients [1–4]. The pathophysiology of CKD-related aortic stiffness is complex and may involve mechanisms such as vascular calcification, modification of vascular extracellular matrix by AGEs, endothelial dysfunction, and vascular inflammation. In our patients, aortic stiffness was abnormal in 50 % of the subjects, as compared to the decade-specific normal values obtained from healthy individuals [22]. PD patients had a statistically nonsignificant higher cf-PWV; however, adjustments for mean blood pressure and baseline imbalances (CVD and smoking status) revealed that PD patient had a higher cf-PWV. In order to examine whether this association is related to higher accumulation of tissue AGEs, we incorporated skin AF into the model, and indeed, we found that the impact of PD on cf-PWV was attenuated and was no longer significant. In the whole cohort, there was a positive association between skin AF and aortic stiffness, even after correction for mean blood pressure. Because age has a strong influence on both skin AF and aortic stiffness, we were not able to see any

added value of skin AF as a determinant for aortic stiffness in our study population.

In contrast, augmentation pressure was positively associated with the skin AF. Even after correction for age and cf-PWV, there was still a positive association between skin AF and wave reflection. The association of augmentation pressure and skin AF, independent of mean blood pressure (modulated by vascular tone), age, and cf-PWV, suggests that there might be a vascular damage and/or remodeling at the level of microcirculation that results in enhanced coefficient of wave reflection. Indeed, the amplitude of wave reflection is not only dependent on stiffness of elastic arteries (macrocirculation), but also on the stiffness of peripheral muscular arteries, vascular tone, and reflecting sites of the microcirculation. Some AGEs can activate receptor for AGE (RAGE) on endothelial cells and vascular smooth muscle cells, activating a number of intracellular pathways that are involved in the production of vasoconstrictive and proinflammatory factors involved in the regulation of vascular tone and vascular remodeling [30–34]. Our observations are in keeping with previous studies suggesting that accumulation of AGEs might have a more observable detrimental impact on smaller vasculature as compared to their impact on larger arteries [35–37].

We conducted a thorough clinical, biochemical, pharmacological, and hemodynamic assessment using validated devices and methodology in a controlled environment. We acknowledge that the small sample size of the study is one limitation. However, the small sample size is counterbalanced by subjects who were well matched for age, gender, and diabetes. Since the study included prevalent dialysis population, which might have been contaminated by survival bias, we aimed and succeeded in properly matching patients based on their dialysis vintage in both groups. Finally, it should be mentioned that other pathways such as endocrine imbalances were not evaluated in the present study [38–40].

In summary, skin AF and cf-PWV were higher in PD patients after adjustment for differences in baseline characteristics. There was a positive association between skin AF and aortic stiffness. Finally, there was a positive association between skin AF and enhanced wave reflection, suggesting a more detectable impact of AGEs on smaller vessels (microcirculation). These observations support the potential role of AGEs-induced vascular disease in dialysis patients.

Acknowledgments This project was supported by the Canadian Institute of Health Research (CIHR), New Emerging Team Grant (NET-54008), the Heart & Stroke Foundation of Canada, the Kidney Foundation of Canada, and the Canadian Diabetes Association. V.C. holds a scholarship from *Fonds de recherche du Québec – Santé (FRQ-S)*, F. M. held a scholarship from Kidney Foundation of Canada, S.D.S. holds a KRESCENT scholarship supported by CIHR, Kidney Foundation of Canada and Canadian Society of Nephrology, and M.A. holds a scholarship from *FRQ-S*.

Conflict of interest The authors report no conflict of interest.

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