Comparison of skin autofluorescence, a marker of tissue advanced glycation end-products in peritoneal dialysis patients using standard and biocompatible glucose containing peritoneal dialysates

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Abstract

Background

Heat sterilisation of peritoneal dialysis (PD) dialysates leads to the generation of advanced glycation products (AGEs), which can then deposit in the skin and be measured by skin autofluorescence (SAF). Newer biocompatible dual chamber dialysates contain less AGEs. We wished to determine whether the use of these newer dialysates resulted in lower SAF.

Methods

SAF was measured using the AGE reader, which directs ultraviolet light, intensity range 300-420 nm (peak 370 nm) in patients established on PD for > 3 months using glucose containing dialysates.

Results

We screened 196 consecutive patients, and measured SAF in 150; 86(57.3%) male, median age 62 (53-71) years, median duration of PD treatment 17 (8.6-34.3) months. The median SAF was 3.48 (2.92-4.26) AU. The median SAF in the 57 (38%) patients prescribed biocompatible dual chamber bag dialysates was 3.39 (2.69-3.98) vs 3.5 (3.05-4.54) for those using standard dialysates (p=0.044). Although prescription of biocompatible fluids was associated with SAF on univariate analysis, but not on multivariable testing, SAF was independently associated with Stoke-Davies co-morbidity grade (β 0.045, 95% confidence limits (CL) 0.015 to 0.075, p=0.002), log duration of PD therapy (β 0.051, CL 0.001 to 0.101, p=0.045), white ethnicity (β 0.066, CL 0.028 to 0.104, p=0.001), and negatively with serum albumin (β -0.006, CL -0.008 to -0.004, p=0.014)

Conclusions

Although SAF was lower in PD patients prescribed biocompatible dual chamber dialysates, on multivariable testing these dialysates were not independently associated with SAF. Other factors than PD fluid AGE content appear more important in determining SAF.

Introduction

Cardiovascular disease remains the leading cause of death for patients with chronic kidney disease and in particular for those with end-stage kidney disease (ESKD) despite advances in dialysis treatments.[1, 2] In addition to the traditional risk factors for cardiovascular disease, dialysis patients also

have additional non-traditional risk factors, including bone mineral disorders, anaemia, uraemic toxins and oxidative stress. Advanced glycation end products (AGEs) are produced by the non-enzymatic reaction between reducing sugars and protein molecules and are normally cleared by the kidney. Accumulation of these compounds increases oxidative reactions, resulting in inflammation and promoting vascular damage, fibrosis and accelerating atherosclerosis.[3]

In the circulation, the plasma concentration of AGEs can vary, falling post-haemodialysis compared to pre-dialysis with high flux and haemodiafiltration treatments and also depending upon the dietary intake of preformed AGEs.[4, 5] However increased circulating AGEs results in tissue deposition, and as such tissue deposits more reliably reflect longer term exposure. Skin autofluorescence (SAF) has been shown to be a reliable, non-invasive measurement of the dermal content of AGEs. Previous studies have reported that hemodialysis patients with higher levels of SAF had greater risk of cardiovascular mortality.[6, 7]

For peritoneal dialysis (PD) patients, glucose is used as the main osmotic agent in dialysate solutions to achieve ultrafiltration. Heat sterilization of these dialysates results in formation of glucose degradation products (GDPs). High level of GDPs in PD dialysate solutions can potentially then lead to increase AGEs in the body.[8, 9] Compared to the standard single chamber dialysates, the newer dual chamber peritoneal dialysate bags, which contain glucose in a much greater acidic solution generate much fewer GDPs when sterilised.[10, 11] Studies using these newer dual chamber lower GDP dialysates have reported less systemic inflammation.[12] We therefore wished to determine whether treatment of PD patients with these dual chamber lower GDP dialysates, which are marketed as being less bio-incompatible reduces tissue AGEs deposition compared to standard dialysates by measuring SAF.

Methods

We measured SAF when PD patients attended university tertiary centre clinics for routine outpatient review. Patients who had been established on PD for less than 3 months, and those not using glucose containing dialysates were excluded. SAF was measured using AGE reader (DiagnOptics, Groningen, Netherlands), which directs ultraviolet light (UV), intensity range 300-420 nm (peak 370 nm), through the skin for excitation AGEs deposited in subcutaneous tissues, and the measured auto-fluorescence light with a spectrophotometer with a range 300-600 nm.[13, 14] The AGE reader was fitted with the additional light source for those with darker skin pigmentation. SAF was measured three times on the volar surface of the dominant arm, adjusted for skin colour (calculated by AGE reader software), and

the average value recorded. All measurements were made by the single observer blinded to whether patients used single or dual chamber dialysates.

Peritoneal membrane assessment was by standard methods with peritoneal transporter status calculated from the four-hour peritoneal dialysate effluent creatinine to serum ratio from a peritoneal equilibration test (PET), weekly urea clearance (Kt/Vurea) and dietary protein nitrogen appearance were calculated by standard methods from 24-hour urine and total peritoneal dialysate effluent samples.[15] Glucose absorption was calculated from the amount of glucose in the fresh dialysate and the measured glucose in the spent peritoneal dialysate. No patient had been treated for PD peritonitis or had a hospital admission within preceding 3 months. Patient dialysed using standard glucose dialysates, icodextrin and dual chamber dialysates (Dianeal, Extraneal Baxter Health Care, Deerfield, Illinois, USA and Balance Fresenius Medical Care, Bad Homberg, Germany). Patients had been maintained on either standard glucose dialysates or the newer dual chamber lower GDP dialysates since initiation of PD.

Blood tests were taken concurrently and analysed by standard laboratory methods for urea, creatinine, albumin, haemoglobin, C-reactive protein (CRP), and glycated haemoglobin [16] Relevant medical history and medications were obtained from hospital computerised records. Patients co-morbidity was assessed using the Davies-Stoke co-morbidity score system.[17] Dietary and smoking history were taken by direct patient questioning.

The observational study was registered with National Health Service (NHS) ethics (IRAS129559) and approved by London Camden and Islington research ethics committee (13/LO/0912) and registered (ISRCTN70556765). In keeping with the declaration of Helsinki, patients were required to provide informed consent.

Statistical analysis

All categorical data are reported as numbers (percentage) and continuous data are presented as mean ± standard deviation or median (interquartile range). Standard statistical tests were used to analyse data (D'Agostino & Pearson normality test, t-test, Mann Whitney U test, Chi square test) with appropriate corrections made for multiple testing. Univariate analysis was by Spearman correlation testing. All variables which were significant on univariate analysis and also those up to $p<0.1$ were then entered into a multivariable step-backward model, with non-parametric variables log transformed if required to improve variable distribution. Variables were then only retained where the 95% confidence intervals for the estimate did not include zero or there was an improvement in model fit (as demonstrated by the -2log likelihood), models were checked for collinearity and variable inflation factor. Statistical analysis used

Statistical Package for Social Science version 24.0 (IBM Corporation, Armonk, New York, USA). Statistical significance was taken as $p<0.05$.

Results

One hundred and ninety-six consecutive PD patients, established on PD for more than 3 months using glucose containing dialysates attended the univeristy PD clinics. We were able to measure SAF in 150 patients; 86(57.3%) male, median age 62 (53-71) years, median duration of PD treatment 17 (8.6-34.3) months. Six (4%) patients were vegetarian. The median SAF was 3.48 (2.92-4.26) AU. We were unable to measure SAF in 46 patients, 28 (60.9%) male, mean age 56.5 ± 15 years, 28 (60.9%) were African or Afro-Caribbean and 14 (30.4%) South Asian. We were able to measure SAF in all White and East Asian patients, 82.3% of South Asian and 22.2% of African or Afro-Caribbean.

Fifty-seven (38%) of the patients with SAF measurement were prescribed dual chamber lower GDP dialysates (Table 1). There was no difference in patient ethnicity between those prescribed dual chamber lower GDP dialysates, either when comparing the different ethnicities ($X2=1.83$, $p=0.87$), or as white vs non-white ethnicity ($X2=0.16$, $p=0.89$). The SAF level was lower in the patients using dual chamber lower GDP dialysates comparing to the ones using standard dialysates (Figure 1). SAF was lower, but not statistically different, in those non-white patients using dual chamber lower GDP dialysates (3.21 ±1.06 vs 3.46 ±0.77 AU), and also white patients (4.05 ±1.06 vs 4.08 ±1.17 AU). Patients using dual chamber lower GDP dialysates used less icodextrin, had dialysed for a shorter period and had greater proportion were non-smokers. There were no differences in sex, age, race, residual renal function, total weekly Kt/Vurea, peritoneal transporter status, peritoneal dialysis modality, glycated haemoglobin, nPNA, diabetes or co-morbidity score between groups.

We then divided patients according to the median SAF of 3.84 AU. There was no difference in patient age, proportion of patients with diabetes, or glycated haemoglobin, or prescription of dextrose dialysates or icodextrin (table 2). However, those patients with higher SAF had lower residual renal function and had been treated by PD for longer.

On univariate analysis SAF was associated with white ethnicity, C reactive protein, diabetes, co-morbidity score and longer treatment with PD and negatively with residual renal function, serum albumin, nPNA and use of icodextrin and dual chamber glucose dialysates (table 3).

We then analysed a multivariable model, and SAF was independently associated with white ethnicity, co-morbidity grade, and longer treatment with PD, and negatively with serum albumin (table 4).

Discussion

Heating glucose in solution leads to the formation of 3 de-oxyglucasone and other glucose degradation products (GDPs) which promote the formation of AGEs.[8] Alternative methods of sterilisation, such as filtration reduce the amounts of GDPs in peritoneal dialysates.[11] Nevertheless heat sterilisation is currently the only method permitted for PD dialysates. However, the amount of GDPs generated by heat sterilisation can be reduced when glucose is heated in an increasingly acidic solution.[11] As such the amount of GDPs are much lower in dual chamber PD dialysates compared to standard single chamber dialysates.[10] Clinical studies have observed that GDPs from the PD dialysates can be transported across the peritoneal membrane, and be detected in serum.[9] Other studies have reported that patients using dual chamber PD lower GDP dialysates have lower levels of systemic inflammation.[12] Circulating AGEs lead to skin deposition, and studies have shown a strong association between skin AGE deposition and SAF.[13] As a number of observational studies have reported an association between SAF and mortality in haemodialysis patients we wished to determine whether the use of dual chamber lower GDP PD dialysates would result in lower SAF.[6, 7]

We found that SAF was significantly lower in PD patients using dual chamber lower GDP PD dialysates compared to standard single chamber glucose dialysates. Patients prescribed the dual chamber lower GDP PD dialysates had borderline lower C reactive protein and greater serum albumin compared to those using standard PD dialysates, which would be in keeping with AGEs as biomarkers of tissue stress. However, patients prescribed dual chamber lower GDP PD dialysates had dialysed for a shorter time period and a greater proportion were non-smokers, and fewer used icodextrin. It is unclear as to whether SAF continues to accumulate with time in PD patients. Importantly there was no difference in residual renal function, PD modality or peritoneal transporter status on multivariate analysis . Studies in haemodialysis patients have reported an increase in patients treated by haemodialysis, but not for those treated by haemodiafiltration.[14] As if the production of AGEs is matched by the additional removal of AGEs with convective clearance during haemodialfiltration, then levels would not be expected to increase, whereas depending upon the dialyzer membrane pore size, then AGEs could accumulate in haemodialysis patients, once residual renal function had been lost.[18] Although some previous reports have demonstrated an association between smoking status and SAF,[19] we were unable to demonstrate an association.

A previous report has suggested that the use of icodextrin dialysates may lead to an increase in SAF [20] Our patients prescribed dual chamber lower GDP dialysates had lower SAF, but they also had lower icodextrin usage. Although icodextrin usage could have potentially introduced bias, when we analysed patients according to SAF, there was no effect of icodextrin.

On univariate analysis, as expected we found a negative association between residual renal urea clearance and SAF, and lower SAF was also associated with lower co-morbidity, lower C reactive protein, higher serum albumin, greater nPNA and use of dual chamber lower GDP dialysates. Although previous reports have suggested that lower protein diets may lead to lower SAF, by reducing dietary preformed AGEs, we suspect that the association with nPNA is linked to healthier fitter patients generating more urea nitrogen, as more active life-styles are recognised to reduce SAF.[5, 21, 22] On the other hand increasing SAF was associated with increasing co-morbidity, diabetes and longer duration of PD therapy. Some previous reports have observed an association with diabetes, although this has not been universal.[6, 23, 24] In our series we measured glycated haemoglobin in all patients and found no association between glycated haemoglobin and SAF. As we report an observational study we were unable to determine whether the increasing SAF with longer duration of PD therapy was due to greater exposure to PD dialysates, or loss of residual renal function.

SAF was greater in patients of white ethnicity. Although the AGE reader is fitted with an additional light source to allow for measurements of SAF in patients with darker skin pigmentation, we were unable to measure SAF in around 17% of South Asian and 78% of African-Afro-Caribbean patients due to very dark skin pigmentation. As there was no difference in the proportion of ethnic minorities between the groups we do not think that this would have biased our results. Some studies have previously reported a lower success rate in measuring SAF in patients with heavily pigmented skin, although others have reported successfully measuring SAF in African-Americans with sickle cell disease, and patients from sub-Saharan Africa.[25-27] SAF is associated with increased mortality for both haemodialysis and PD patients,[7, 28] and observational studies from North America, United Kingdom and Demark all report increased mortality for white dialysis patients compared to those from the ethnic minorities.[29-31]

We report an observational study, and although there was a difference in SAF between those patients prescribed dual chamber lower GDP glucose containing dialysates, on multivariable testing, this difference no longer remained statistically significant. Previous reports have noted that prescription of these dialysates leads to a reduction in biomarkers of systemic inflammation, and endothelial dysfunction,[12] and others lower peritoneal effluent cancer antigen 125 and ultrafiltration volumes, suggestive of less intra-peritoneal inflammation.[32] Our patients prescribed dual chamber lower GDP PD

dialysates had marginally higher serum albumin and lower C reactive protein levels, and we are unable to determine whether this was consequent upon the dialysate prescribed. In addition, the patients treated by dual chamber lower GDP PD dialysates had been treated with PD for a shorter PD time, although residual urinary urea clearances were not different.

Our study would suggest that although the use of dual chamber lower GDP PD dialysates may appear to lead to lower accumulation of AGEs resulting in lower SAF, we found that in our cross-sectional study that other factors than the choice of PD dialysate were more important in determining SAF, such as duration of PD treatment, residual renal function, patient co-morbidity and serum albumin.

Fig. 1 Difference in skin autofluorescence (SAF) between using standard dialysates and dual chamber lower glucose degradation product dialysates in peritoneal dialysis patients. * $p < 0.05$

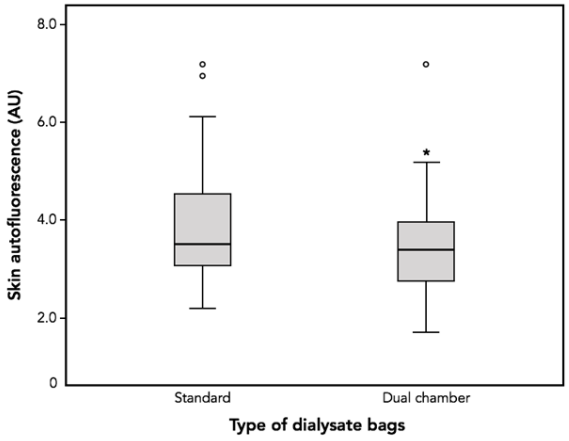

Table 1 Patients demographic using dual chamber bag low glucose degradation product (GDP) dialysates compared to those using single bag dialysates. Values presented as percentage, mean ± standard deviation or median (interquartile range). Body mass index (BMI), peritoneal equilibration test (PET), dialysate (D), plasma (P), automated peritoneal dialysis cycler (APD), continuous ambulatory peritoneal dialysis (CAPD), glycated haemoglobin (HbA1C), C-reactive protein (CRP), normalised protein nitrogen appearance rate (nPNA). Results as integer, percentage, mean ± standard deviation or median (interquartile range). p values vs single chamber glucose dialysate group.

Variables	Overall (N=150)	Single bag (N=93)	Dual chamber low GDP(N=57)	P-value
Male (%)	86 (57.3)	53 (57.0)	33 (57.9)	0.913
Age, years	62 (53-71)	63.5 (55.3-73.7)	59 (50.5-69.0)	0.240
Smoking status (%)				0.002
- Never	102 (69.4)	54 (60)	48 (84.2)	
- Ex-smoker	17 (11.6)	11 (12.2)	6 (10.5)	
- Current smoker	28 (19)	25 (27.8)	3 (5.3)	
Race (%)				0.131
- White	63 (42)	44 (47.3)	19 (33.3)	
- South Asian	65 (43.3)	36 (38.7)	29 (50.9)	
- Others	22 (14.7)	15 (14)	9 (14.1)	
BMI	27.1 ± 4.9	26.5 ± 4.79	28.2 ± 5.11	0.147
DM (%)	59 (39.3)	38 (40.9)	21 (36.8)	0.625
Davies comorbidity (%)				0.108
- Grade 0	56 (37.3)	29 (31.2)	27 (47.4)	
- Grade 1	79 (52.7)	55 (59.1)	24 (42.1)	
- Grade 2	15 (10)	9 (9.7)	6 (10.5)	
Icodextrin usage (%)	103(68.7)	70(75.3)	33(57.9)	0.026
Dialysis vintage, months	17 (8.62-34.25)	21.5(12-38.75)	14.04(4.58-31.96)	0.007
Weekly Kt/Vurea				
- Total	1.92(1.55-2.42)	1.92(1.59-2.44)	2.06(1.50-2.42)	0.593
- residual Renal Kt/Vurea	0.57(0.10-1.25)	0.45(0.08-0.96)	0.79(0.17-1.33)	0.072
- peritoneal Dialysis Kt/Vurea	1.30(1.00-1.59)	1.37(1.12-1.63)	1.23(0.86-1.44)	0.001
Urine volume, ml/day	600(344.8-1304.3)	508(100-833.8)	850(312.5-1400)	0.054
PET 4 hr D/Pcreatinine	0.68 ± 0.14	0.72 ± 0.13	0.62 ± 0.12	<0.001
Peritoneal Dialysis mode				0.242
- CAPD (%)	16 (10.7)	11 (11.8)	5 (8.8)	

- APD dry day (%)	41 (27.3)	21 (22.6)	20 (35.1)	
- APD wet day (%)	93 (62)	61 (65.6)	32 (56.1)	
Serum albumin, g/L	38.13 ± 4.3	37.6 ± 4.01	39 ± 4.66	0.051
HbA1C, mol/mmol	40.5(35-55.2)	41(36.6-55.2)	38.5(33-57.25)	0.255
CRP, mg/L	4(2-12)	5(2-16.75)	3.5(1-10)	0.050
nPNA, g/kg/day	0.92(0.69-1.12)	0.90(0.70-1.12)	0.96(0.69-1.11)	0.668

Table 2. Peritoneal Dialysis (PD) patients divided into those with higher and lower skin autofluorescence (SAF). Combined 24 hour urinary urea and creatinine clearance (residual renal function), Glycated haemoglobin (HbA1c). Values as integers (percentage), or median (interquartile range).

Variable	Higher SAF	Lower SAF	p value
number	73	77	
SAF AU	4.27 (3.93-4.83)	2.95 (2.48-3.27)	<0.001
Age years	63 (55-71)	61 (50-72)	>0.05
Residual renal function mL/min/1.73m^2	0.7 (0.2-2.0)	1.4 (0.5-2.7)	0.039
PD vintage months	22.7 (12.1-41.2)	12.1 (5.4-31.4)	0.001
Glucose exposure g/day	146 (106-204)	129 (98-182)	>0.5
Diabetic (%)	31 (42.6)	28 (36.4)	>0.05
HbA1c mol/mmol	41 (35.5-55.2)	39.9 (34.4-56.1)	>0.05
Icodextrin prescribed (%)	50 (68.5)	53 (68.3)	>0.05

Table 3 Spearman univariate analysis for factors associated with skin autofluorescence. Glucose degradation products (GDP).

Variables	r	P-value
White ethnicity	0.323	<0.001
Smoking status	0.141	0.088
Diabetes mellitus	0.182	0.026
Davies comorbidity grade	0.260	0.001
Months of peritoneal dialysis treatment	0.298	<0.001
24 hour urinary Kt/Vurea	-0.221	0.008
Serum albumin	-0.375	<0.001
Serum C-reactive protein	0.278	0.001
Normalised protein nitrogen appearance	-0.229	0.008
Dual chamber low GDP glucose dialysates	-0.165	0.044

Table 4 Multivariable model for log skin autofluorescence. Standard error β (StE β), standardised β (St β), 95% confidence intervals (95% CI). Model fit r^2= 0.286, adjusted r^2= 0.263.

Variables	β	StE β	St β	t	95% CI	P-value
Serum albumin	-0.006	0.002	-0.203	-2.483	-0.008 to -0.004	0.014
Stoke-Davies grade	0.045	0.015	0.244	3.128	0.015 to 0.075	0.002
White ethnicity	0.066	0.019	0.277	3.471	0.028 to 0.104	0.001
Log dialysis vintage	0.051	0.025	0.163	2.029	0.001 to 0.101	0.045

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