LONGITUDINAL TREND IN LIPID PROFILE OF INCIDENT PERITONEAL DIALYSIS PATIENTS IS NOT INFLUENCED BY THE USE OF BIOCOMPATIBLE SOLUTIONS

Yeoungjee Cho,^{1,2,3} Janine Büchel,⁴ Sonja Steppan,⁴ Jutta Passlick-Deetjen,⁵ Carmel M. Hawley,^{1,2,3} Goce Dimeski,^{2,6} Margaret Clarke,⁷ and David W. Johnson,^{1,2,3} on behalf of the balANZ Trial Investigators

Department of Renal Medicine,¹ Princess Alexandra Hospital, Brisbane, Australia; School of Medicine,² University of Queensland, Brisbane, Australia; Translational Research Institute,³ Brisbane, Australia; Fresenius Medical Care Deutschland,⁴ Bad Homburg, Germany; Department of Nephrology,⁵ University Clinic, Duesseldorf, Germany; Department of Chemical Pathology,⁶ Pathology Queensland, Princess Alexandra Hospital, Brisbane, Australia; and Fresenius Medical Care,⁷ Sydney, Australia

◆ **Background:** The longitudinal trends of lipid parameters and the impact of biocompatible peritoneal dialysis (PD) solutions on these levels remain to be fully defined. The present study aimed to a) evaluate the influence of neutral pH, low glucose degradation product (GDP) PD solutions on serum lipid parameters, and b) explore the capacity of lipid parameters (total cholesterol [TC], triglyceride [TG], high density lipoprotein [HDL], TC/HDL, low density lipoprotein [LDL], very low density lipoprotein [VLDL]) to predict cardiovascular events (CVE) and mortality in PD patients.

◆ **Methods:** The study included 175 incident participants from the balANZ trial with at least 1 stored serum sample. A composite CVE score was used as a primary clinical outcome measure. Multilevel linear regression and Poisson regression models were fitted to describe the trend of lipid parameters over time and its ability to predict composite CVE, respectively.

◆ **Results:** Small but statistically significant increases in serum TG (coefficient 0.006, $p < 0.001$), TC/HDL (coefficient 0.004, $p = 0.001$), and VLDL cholesterol (coefficient 0.005, $p = 0.001$) levels and a decrease in the serum HDL cholesterol levels (coefficient -0.004, $p = 0.009$) were observed with longer time on PD, whilst the type of PD solution (biocompatible vs standard) received had no significant effect on these levels. Peritoneal dialysis glucose exposure was significantly associated with trends in TG, TC/HDL, HDL and VLDL levels. Baseline lipid parameter levels were not predictive of composite CVEs or all-cause mortality.

◆ **Conclusion:** Serum TG, TC/HDL, and VLDL levels increased and the serum HDL levels decreased with increasing PD duration. None of the lipid parameters were significantly modified by biocompatible PD solution use over the time period studied or predictive of composite CVE or mortality.

KEY WORDS: Biocompatible; cardiovascular events; glucose degradation products; lipid; mortality; peritoneal dialysis.

Premature cardiovascular events (CVE) are a leading cause of mortality in patients with end-stage kidney disease (ESKD) receiving peritoneal dialysis (PD) (1). Some of the risk factors of CVE in ESKD include inflammation and dyslipidemia (2–4). The plasma lipid profile commonly evolves during the progression of chronic kidney disease, especially in PD patients in whom elevated serum total cholesterol (TC), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol, triglyceride (TG), and a decrease in high-density lipoprotein (HDL) levels are frequently reported (4–6). These changes are pro-atherogenic and may contribute to an increased burden of CVE in patients with ESKD.

Some of the lipid profile changes in PD patients have been attributed to the use of glucose-based PD solutions (7). Indeed, several observational studies have reported an improvement in lipid profile (i.e. reduction in TC) with the use of glucose-free PD solution products (8–10). These results have been further substantiated by combined results from the IMPENDIA and EDEN randomized controlled trials (RCTs), whereby the use of a glucose-sparing PD regimen led to a significant decrease in serum TG and VLDL levels (11).

Serum lipids in PD patients may also be impacted by glucose degradation product (GDP) exposure through dialysis solutions. Compared with conventional solutions, neutral-pH, low-GDP solutions have been shown to result in lower serum concentrations of advanced glycation end-products (AGE) (12,13), which in turn have been associated with lower serum concentrations of TG and LDL and higher concentrations of HDL (14,15). Our group has also previously demonstrated uniform down-regulation of cholesterol biosynthesis pathway genes in human peritoneal mesothelial cells following exposure to these fluids (S. Steppan, unpublished observations).

The aims of the present study were to describe the longitudinal trend in lipid profile in a well-defined cohort of PD patients and explore the utility of these markers as a predictor

Perit Dial Int 2016; 36(2):146–153 epub ahead of print: 01 Oct 2015
<http://dx.doi.org/10.3747/pdi.2014.00291>

Correspondence to: David Johnson, Department of Nephrology, Level 2, ARTS Building, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, Qld 4102, Australia.

david.johnson2@health.qld.gov.au

Received 8 January 2015; accepted 3 February 2015.

Supplemental material available at www.pdconnect.com

of CVE and mortality in this patient group. In addition, it was to explore whether the use of more biocompatible PD solutions might impact on the serum lipid parameters.

METHODS

STUDY POPULATION

Data were obtained from the participants of the balANZ trial (16). A detailed description of the study design and methodology has been previously published (17), as have the results of the main primary and secondary analyses (16,18–21). The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12606000044527). Of the 185 participants in the balANZ trial, 175 participants (Balance [Fresenius Medical Care North America, Waltham, MA, USA] $n = 86$; Stay.Safe [Fresenius Medical Care North America, Waltham, MA, USA] $n = 89$) who had at least 1 serum sample stored during trial participation were included in the present investigation.

LIPID MEASUREMENTS

Serum samples were collected at baseline, 6-, 12-, 18- and 24-month visits. Serum was immediately stored at -20°C or in a -80°C freezer locally and transported frozen to a central storage facility and kept in a -80°C freezer. Total cholesterol, TG and HDL were measured on the Beckman Dx C800 general chemistry analysers (Beckman Coulter, Brea, CA, USA) while the LDL and VLDL were calculated.

CLINICAL OUTCOME MEASUREMENTS

The primary clinical outcome measure was number of episodes of a composite CVE as defined previously (20). A secondary clinical outcome measure was all-cause mortality during the study duration.

STATISTICAL ANALYSIS

Results were expressed as frequencies (percentages) for categorical variables, mean $\pm$ standard deviation (SD) for continuous normally distributed variables, and median (interquartile range) for continuous non-normally distributed variables. Differences between groups on baseline characteristics were analyzed by χ^2 test for categorical data, t -test for continuous normally distributed data and Mann-Whitney U test for continuous non-normally distributed data. Trends in lipid parameters over the follow-up period were analyzed using a multilevel linear regression model. Continuous time was included as a predictor variable. Random intercepts and slopes were added to allow for repeated measurements over time. To evaluate the differences between the 2 treatment groups on individual lipid parameters, PD solution type and a variable representing the interaction between solution type and time were subsequently added to the model as predictor variables. If

the interaction was not statistically significant, it was dropped from the model. Non-linear effect of time was explored by reapplying the model using time as a categorical variable. The lipid parameter data were log-transformed due to their non-normal distributions. Although the baseline lipid parameter data were missing in only 3% of participants, there was a substantial amount of missing lipid parameter data overall (28%). As sensitivity analyses, the multilevel linear regression model was applied in the subgroup with complete lipid parameter data (i.e. those with 5 measurements; biocompatible $n = 33$; control $n = 39$) and the effect of glucose loading from PD solutions used (g/day) was explored as a time-varying covariate.

To determine whether each individual lipid parameter predicted composite CVE, a multilevel Poisson regression model was fitted to the CVE counts. The event counts of composite CVEs were recorded at 6-monthly intervals from baseline to 24 months, providing each participant with up to 4 values for composite CVEs. Baseline lipid parameter, clinically recognized risk factors of CVE (i.e. age, ethnicity, body mass index, co-morbidities, baseline glomerular filtration rate [GFR]), and randomly assigned type of PD solution were included as fixed effects in an initial full model. Random effects (subject, time) were added to allow for repeated measurements over time. History of dyslipidemia was available but was not included to avoid over-adjustment. Variables with statistically non-significant effects were not included in the final model. Backwards selection method was adopted (i.e. 1 at a time) with a sequential removal of variables, comparing the new model with the old model using the log likelihood ratio test. The fit of the final model was checked against the full model using the likelihood ratio test. Each individual lipid parameter, as a predictor of all-cause mortality, was modeled using exact logistic regression. Due to a low event number ($n = 17$), only the results from univariable analyses of baseline lipid parameter for each subject were presented. Data were analyzed using the software packages Stata/SE12.1 (College Station, TX, USA). $P < 0.05$ was considered to represent a statistically significant result.

RESULTS

PATIENT CHARACTERISTICS

The patients (biocompatible, $n = 86$; standard, $n = 89$) were well matched for all baseline characteristics, including serum lipid parameters (Table 1). The baseline characteristics of this subgroup have been published previously (20), and were comparable to those for the original balANZ trial cohort (16).

THE TREND OF SERUM LIPID PARAMETERS

Serum TG, VLDL, and TC/HDL concentrations increased with longer PD duration, whilst serum TC levels remained relatively stable following an initial increase at month 6 (Table 2). When a multilevel linear regression model was fitted, statistically significant increases in the linear trends of

TABLE 1
Baseline Patient Characteristics

Characteristic	Total (<i>n</i> =175)	Biocompatible (<i>n</i> =86)	Control (<i>n</i> =89)	<i>P</i> values
Age (yrs)	61 (50–69)	63.5 (49–69)	60 (50–68)	0.51
Female	77 (44)	36 (41)	41 (46)	0.58
Ethnicity				
Caucasian	140 (80)	73 (85)	67 (75)	0.42
Aboriginal and Torres Strait Islander	3 (2)	1 (1)	2 (2)	
Asian	22 (13)	9 (10)	13 (15)	
Maori and Pacific Islander	10 (5)	3 (3)	7 (8)	
Cardiovascular disease	143 (82)	66 (77)	77 (87)	0.10
Diabetes mellitus	58 (33)	27 (31)	31 (35)	0.63
Medications				
Antiplatelet	71 (41)	31 (36)	40 (45)	0.23
Renin-angiotensin blockade	104 (59)	53 (62)	51 (57)	0.56
β -blocker	73 (42)	34 (40)	39 (44)	0.57
Statin	107 (61)	54 (63)	53 (60)	0.66
Body mass index (kg/m ²)	27.25 (23.80–31.37)	27 (23.82–30.25)	27.58 (23.70–31.82)	0.45
Initial PD modality				
Continuous ambulatory PD	156 (89)	76 (88)	80 (90)	0.75
Automated PD	19 (11)	10 (12)	9 (10)	
GFR (mL/min per 1.73m ²)	6.85 (5.40–8.90)	6.88 (5.90–9.00)	6.84 (5.00–8.60)	0.28
Urine volume (mL/d)	1,369 (982–1,890)	1,436 (971–1,897)	1,360 (1,020–1,870)	0.75
Serum albumin (g/L)	37.38 $\pm$ 5.29	37.97 $\pm$ 4.80	36.82 $\pm$ 5.69	0.15
Hemoglobin (g/L)	113.5 (103–126)	111 (101–127)	114 (103–126)	0.85
Lipid parameters*				
Total cholesterol (mmol/L)	4.2 (3.5–5.0)	4.1 (3.4–5.0)	4.3 (3.6–5.1)	0.47
Triglyceride (mmol/L)	1.9 (1.3–2.6)	1.9 (1.4–2.5)	1.9 (1.3–2.7)	0.83
HDL (mmol/L)	1.0 (0.9–1.3)	1.0 (0.9–1.3)	1.0 (0.9–1.3)	0.63
Total cholesterol/HDL	3.8 (3.1–4.8)	3.7 (3.0–5.2)	3.8 (3.1–4.8)	0.84
LDL (mmol/L)	2.1 (1.7–2.8)	2.1 (1.5–2.6)	2.0 (1.7–2.9)	0.82
VLDL (mmol/L)	0.8 (0.6–1.1)	0.9 (0.6–1.2)	0.8 (0.6–1.1)	0.38

PD = peritoneal dialysis; GFR = glomerular filtration rate; HDL = high density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein.

* No. of samples measured *n*=169 (biocompatible *n*=82; control *n*=87). To convert mmol/L to mg/dL, multiply by 38.66 for total cholesterol, HDL, LDL, and VLDL; and multiply by 88.6 for triglyceride.

TG (coefficient 0.006, *p* < 0.001; 2.8 mmol/L vs 2.3 mmol/L [mean]), TC/HDL (coefficient 0.004, *p* = 0.001; 5.6 vs 4.3), and VLDL (coefficient 0.005, *p* = 0.001; 1 mmol/L vs 0.9 mmol/L) were observed over time, whilst HDL demonstrated a decreasing trend (coefficient -0.004, *p* = 0.009; 1.0 mmol/L vs 1.1 mmol/L; Figure 1). However, these associations were no longer evident when the glucose exposure from PD solutions was explored as a time-varying covariate for TC/HDL (coefficient 0.003, *p* = 0.05) and HDL (coefficient -0.001, *p* = 0.32). The longitudinal trends of all analyzed lipid parameters were comparable between the 2 groups (Table 3; Figure 2). As there was no significant interactive effect of PD solution type and PD duration on each analyzed lipid parameter, solution type was analyzed as an unconditional effect. When time was explored as a categorical variable (Supplementary Table 1), there was a significant increase in TC at months 6 (*p* = 0.001) and 12 (*p* = 0.02), largely driven by a greater increment in TG. Furthermore, a decrease in HDL only reached a statistical level

of significance at months 18 (*p* = 0.005) and 24 (*p* = 0.045). The sensitivity analysis performed in the subgroup in whom a full set of lipid parameters were available (*n* = 72) produced a similar pattern of results (Table 3) except for TG (*p* = 0.06) and VLDL (*p* = 0.21) where the trends no longer reached the level of statistical significance. Similarly, when the glucose exposure from PD solutions was explored as a time-varying covariate, it was a significant predictor of TG (*p* < 0.001), HDL (*p* < 0.001), TC/HDL (*p* = 0.004), and VLDL (*p* = 0.003) levels (Supplementary Table 2). The addition of glucose exposure to the model abolished the association between PD duration and serum HDL (*p* = 0.32) and TC/HDL levels (*p* = 0.05).

LIPID PARAMETER AS PREDICTOR OF COMPOSITE CARDIOVASCULAR EVENTS

A total of 52 composite CVEs were observed in 38 patients (Biocompatible *n* = 19; Control *n* = 19). There were 20 (38%),

TABLE 2
Trend in Lipid Parameters (Median [Interquartile Range])

Lipid Parameter	PD Solution	0 months	6 months	12 months	18 months	24 months
Total cholesterol (mmol/L)	Balance	4.1 (3.4–5.0)	4.5 (3.6–5.5)	4.2 (3.4–5.2)	4.3 (3.4–5.5)	4.1 (3.3–4.9)
	Stay-safe	4.3 (3.6–5.1)	4.6 (3.7–5.4)	4.6 (3.7–5.3)	4.2 (3.6–5.9)	4.3 (3.3–5.9)
Triglyceride (mmol/L)	Balance	1.9 (1.4–2.5)	2.3 (1.7–3.1)	2.3 (1.7–3.3)	2.6 (1.9–3.5)	2.4 (2.1–3.1)
	Stay-safe	1.9 (1.3–2.7)	2.2 (1.6–2.9)	2.5 (1.9–3.7)	2.1 (1.6–3.8)	2.0 (1.6–2.8)
HDL (mmol/L)	Balance	1.0 (0.9–1.3)	1.0 (0.8–1.2)	1.0 (0.8–1.1)	1.0 (0.7–1.2)	1.0 (0.9–1.1)
	Stay-safe	1.0 (0.9–1.3)	1.1 (0.9–1.3)	0.9 (0.8–1.2)	1.0 (0.8–1.2)	1.1 (0.8–1.3)
Total cholesterol/HDL	Balance	3.7 (3.0–5.2)	4.4 (3.4–5.9)	4.4 (3.5–5.7)	4.5 (3.5–5.6)	4.2 (3.3–5.4)
	Stay-safe	3.8 (3.1–4.8)	4.2 (3.3–5.5)	4.6 (3.5–5.9)	4.5 (3.5–5.6)	4.1 (2.9–5.4)
LDL (mmol/L)*	Balance	2.1 (1.5–2.6)	2.1 (1.6–3.2)	1.9 (1.4–3.0)	1.9 (1.5–2.8)	1.8 (1.3–2.4)
	Stay-safe	2.0 (1.7–2.9)	2.4 (1.4–3.3)	2.3 (1.6–2.9)	2.1 (1.7–3.6)	2.0 (1.4–3.5)
VLDL (mmol/L)*	Balance	0.9 (0.6–1.2)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	1.0 (0.8–1.4)	1.1 (0.9–1.3)
	Stay-safe	0.8 (0.6–1.1)	1.0 (0.7–1.3)	1.0 (0.8–1.5)	0.9 (0.7–1.4)	0.9 (0.7–1.2)

PD = peritoneal dialysis; HDL = high density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein.

Number of samples at month 0 (Balance $n=82$; Stay-safe $n=87$), month 6 (Balance $n=72$; Stay-safe $n=73$), month 12 (Balance $n=58$; Stay-safe $n=61$), month 18 (Balance $n=50$; Stay-safe $n=58$), and month 24 (Balance $n=41$; Stay-safe $n=44$).

* No. of samples for LDL and VLDL for Balance and Stay-safe groups at month 0 (82, 80), month 6 (69, 65), month 12 (54, 53), month 18 (44, 51), and month 24 (36, 40). To convert mmol/L to mg/dL, multiply by 38.66 for total cholesterol, HDL, LDL, and VLDL; and multiply by 88.6 for triglyceride.

Figure 1 — Overall trend of log-transformed lipid parameters over time in incident peritoneal dialysis patients (total cholesterol [TC] $p=0.84$; triglyceride [TG] $p<0.001$; high density lipoprotein [HDL] $p=0.009$; TC/HDL $p=0.001$; Low density lipoprotein [LDL] $p=0.18$; Very low density lipoprotein [VLDL] $p=0.001$).

TABLE 3
Multilevel Linear Regression to Evaluate the Effect of Peritoneal Dialysis Solution Type on Serum Lipid Parameters¹

	Variable	All patients (n=175)			Complete patients (n=72) ²		
		Regression coefficient	95% confidence interval	p values	Regression coefficient	95% confidence interval	p values
Log ₁₀ Total Cholesterol	PD solution	Reference	Reference	Reference	Reference	Reference	Reference
	Control	Reference	Reference	Reference	Reference	Reference	Reference
	Biocompatible	-0.02	-0.09–0.05	0.57	-0.07	-0.17–0.04	0.23
Log ₁₀ Triglyceride	Time	0.0002	-0.001–0.002	0.84	-0.0008	-0.003–0.001	0.43
	PD solution	Reference	Reference	Reference	Reference	Reference	Reference
	Control	Reference	Reference	Reference	Reference	Reference	Reference
Log ₁₀ HDL	Biocompatible	-0.02	-0.17–0.12	0.75	-0.01	-0.24–0.21	0.90
	Time	0.006	0.003–0.009	<0.001	0.004	-0.0001–0.007	0.06
	PD solution	Reference	Reference	Reference	Reference	Reference	Reference
Log ₁₀ TC/HDL	Control	Reference	Reference	Reference	Reference	Reference	Reference
	Biocompatible	-0.01	-0.13–0.11	0.87	0.009	-0.19–0.21	0.93
	Time	-0.004	-0.006 to -0.0009	0.009	-0.004	-0.007 to -0.0008	0.01
Log ₁₀ LDL	PD solution	Reference	Reference	Reference	Reference	Reference	Reference
	Control	Reference	Reference	Reference	Reference	Reference	Reference
	Biocompatible	-0.02	-0.13–0.10	0.77	-0.10	-0.29–0.09	0.29
Log ₁₀ VLDL	Time	0.004	0.002–0.006	0.001	0.003	0.00006–0.006	0.045
	PD solution	Reference	Reference	Reference	Reference	Reference	Reference
	Control	Reference	Reference	Reference	Reference	Reference	Reference
Log ₁₀ VLDL	Biocompatible	-0.01	-0.15–0.13	0.89	-0.12	-0.34–0.10	0.29
	Time	-0.002	-0.005–0.001	0.18	-0.004	-0.008–0.0005	0.08
	PD solution	Reference	Reference	Reference	Reference	Reference	Reference
Log ₁₀ VLDL	Control	Reference	Reference	Reference	Reference	Reference	Reference
	Biocompatible	0.03	-0.08–0.14	0.61	0.09	-0.06–0.24	0.25
	Time	0.005	0.002–0.008	0.001	0.002	-0.001–0.006	0.21

PD = peritoneal dialysis; HDL = high density lipoprotein; TC = total cholesterol; LDL = low density lipoprotein; VLDL = very low density lipoprotein.

¹ No statistically significant interaction between PD solution and time on PD.

² Patients with complete lipid data (i.e. those with 5 measurements; Biocompatible n=33; Control n=39).

11 (21.2%), 13 (25%), and 8 (15%) composite CVE episodes recorded at 6, 12, 18, and 24 months, respectively. Composite CVEs were significantly and independently associated with older age (incidence rate ratio [IRR] per year 1.03, 95% CI 1.00 – 1.06, *p* = 0.03) and diabetes mellitus (IRR 2.10, 95% CI 1.04 – 4.26, *p* = 0.04). None of the lipid parameters were associated with composite CVE.

LIPID PARAMETER AS PREDICTOR OF ALL-CAUSE MORTALITY

On univariable exact logistic regression analysis, baseline lipid parameters were not significantly associated with all-cause mortality (TC: odds ratio [OR] 0.93, 95% CI 0.57 – 1.45, *p* = 0.78; TG: OR 0.92, 95% CI 0.60 – 1.28, *p* = 0.77; HDL: OR 0.29, 95% CI 0.06 – 1.22, *p* = 0.10; TC/HDL: OR 1.08, 95% CI 0.89 – 1.29; *p* = 0.34; LDL: OR 1.08, 95% CI 0.63 – 1.74, *p* = 0.75; VLDL: OR 1.22, 95% CI 0.35 – 3.92, *p* = 0.74). Comparable results were observed when baseline lipid parameters were categorized in tertiles (data not shown).

DISCUSSION

The present investigation is the first study to examine the effect of neutral pH, low GDP PD solution on the longitudinal trends of lipid parameters in incident PD patients. A small but statistically significant increase in the serum TG, TC/HDL, and VLDL levels and a decrease in the serum HDL levels with longer time on PD were observed whilst the type of PD solution received had no significant effect on these levels. The majority of the increment in lipid parameters occurred in the first 6 months of the study. Glucose exposure from PD solution use was associated with longitudinal trends in a number of lipid parameters including TG, HDL, TC/HDL, and VLDL and appeared to completely account for the effect of PD duration on HDL and TC/HDL. Baseline lipid parameters levels were not predictive of composite CVEs or all-cause mortality.

Renal insufficiency is frequently accompanied by a secondary form of dyslipidemia attributed to abnormal lipid metabolism in the presence of progressive uremia (22). The predominant features include an increase in the serum TG and

Figure 2 — Trend of log-transformed lipid parameters over time by type of peritoneal dialysis solution received (Biocompatible, $n=86$; Control, $n=89$). TC = total cholesterol; TG = triglyceride; HDL = high density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein.

VLDL levels with low HDL levels and typically LDL levels within a normal range (22,23). Once patients develop ESKD and commence dialysis, the pattern of dyslipidemia undergoes further modification. Little and colleagues conducted one of the largest ($n = 111$) and the longest follow-up (median 37 months) observational studies in incident PD patients and reported a significant increase in TC (5.8 ± 1.51 mmol/L vs 7.06 ± 1.47 mmol/L, $p < 0.05$) levels (24). This study illustrated the ‘pure’ lipid trend in PD patients by not allowing any lipid-lowering therapy to be initiated during the study period. However, it was restricted to continuous ambulatory PD (CAPD) patients from a single center and the statistical approach adopted could have weakened the power of the analyses due to a large number of drop-outs (80%) during the follow-up period (24). Similarly, an increase in TG and a decrease in HDL levels with longer PD duration were reported in a retrospective observational study conducted in non-diabetic incident PD patients ($n = 195$) (7). The present investigation is the largest prospective longitudinal study to date describing the trend of lipid profiles in incident PD patients. In order to account for the correlated data structure from repeated measurements over time, a mixed effects modeling approach was used, which allowed for further covariate adjustments such as the type of PD solutions received

and glucose exposure from PD solutions. A small but statistically significant increase in the linear trends of serum TG, TC/HDL, and VLDL levels and a decrease in serum HDL levels with longer time on PD were observed whilst the type of PD solution (biocompatible vs standard) received had no significant effect on these levels. Comparable levels of systemic inflammation may have partly contributed to a lack of difference between the biocompatible and standard PD solutions (20). In addition, the present study observed ‘early’ increments in TC, TG, and TC/HDL and a ‘late’ reduction in HDL, in keeping with results from other studies (7,24).

Although previous studies have suggested that exposure to low GDP PD solutions might down-regulate cholesterol biosynthesis and result in lower serum AGE levels (which are in turn associated with improved lipid profiles), no differences in serum lipid parameters were observed between patients receiving low GDP solutions and those receiving conventional solutions in the current study. However, glucose exposure from PD solutions was found in this study to be associated with longitudinal trends of several lipid parameters (e.g. TG, HDL, TC/HDL, and VLDL), and appeared to completely account for the effect of PD duration on HDL and TC/HDL levels. These results are in keeping with the general consensus in that

hyperlipidemia seen in PD patients largely relates to continuous absorption of glucose from PD solutions used (25). For example, Jiang and colleagues have demonstrated significant associations between abnormal lipid parameters (increased TG [$p < 0.01$], decreased HDL [$p < 0.01$]) and peritoneal glucose exposure in non-diabetic PD patients (7), whereas others have reported an improvement in the lipid profile (decrease in TC, TG, LDL, and VLDL) following the use of glucose-free PD solutions (e.g. 7.5% icodextrin) (8–11). Although Li and Fengxian concluded in their study a lack of association between glucose concentration in the PD solution and lipid profile in CAPD patients, the 24-h glucose loading from PD solutions was positively correlated with TG ($r = 0.159$, $p < 0.05$) and negatively associated with HDL levels ($r = -0.166$, $p < 0.05$) (26). Therefore, based on the available evidence to date, glucose exposure but not GDP content from PD solutions appears to play a significant role in influencing the abnormal lipid profile in these patients. However, the use of glucose-sparing regimens using amino-acid based PD solutions in combination with icodextrin were associated with an increased rate of serious adverse events, including death, and thus are not routinely recommended (11). Alternative options combining a biocompatible solution with its proven benefits (27) and an adapted automated PD (aAPD) regimen (28) may be a future option that needs to be further investigated.

In contrast to our previous study where baseline interleukin-6 was identified to be a significant and independent predictor of composite CVEs (20), none of the lipid parameters analyzed demonstrated a significant independent association. This is surprising because the presence of dyslipidemia was a significant predictor of composite CVE (20) and has been associated with a higher risk of mortality (24,29). Some of the differences might relate to a relatively high usage of statins in these patients (61%), and therefore the lipid levels measured had less impact on CVEs. Furthermore, the missing predictor variable over time and a low death rate in the present investigation restricted analyses to explore the predictive ability of baseline lipid parameters, which could have lowered the statistical power.

The present study is strengthened by its sample size in comprehensively described cohorts who were participants in a well-controlled RCT. It is one of the largest studies and the first study to examine the impact of biocompatible PD solution use on lipid parameters in incident PD patients. Nonetheless, the conclusions that can be drawn from this study are challenged by several limitations. First, the balANZ trial was an RCT with the primary outcome measure of residual renal function decline, rather than a biomarker study. Therefore, the samples analyzed were not from fasting specimens, which could have affected the measured results. Second, even though it is one of the largest studies to date, the sample size was relatively small with fairly low event numbers in the context of a substantial proportion of missing data on serum lipid parameter levels. This could have weakened the statistical power and placed restrictions on the ability to examine each lipid parameter as a time-varying covariate in predicting composite CVEs. Third, the LDL and

VLDL levels were calculated rather than measured, such that LDL and VLDL levels could not be estimated in patients in whom TG levels were greater than 4.5 mmol/L. Furthermore, the quality of lipids was not assessed (i.e. oxidized LDL). Fourth, subgroup analyses based on medication usage (e.g. statin, fibrate, angiotensin converting enzyme inhibitor), intercurrent illness, or diabetic status could not be performed due to inadequate statistical power. Finally, there were no available data pertaining to the level of proteinuria, peritoneal protein excretion, or dietary intake that could have influenced the measured lipid parameter results independent of PD.

In conclusion, the results of this study demonstrated significant increases in linear trends of serum TG, TC/HDL, and VLDL levels and a decrease in serum HDL levels with increasing PD duration. The majority of increment in TC, TG, TC/HDL, and VLDL occurred in the first 6 months of PD whereas a significant reduction in HDL was only evident beyond 18 months. The longitudinal trends of lipid parameters did not differ significantly between patients receiving biocompatible or standard PD solutions, but PD glucose exposure was significantly associated with trends in TG, TC/HDL, HDL, and VLDL levels. Baseline lipid parameter levels were not predictive of composite CVEs or all-cause mortality. However, the ability to draw definitive conclusions regarding the effects of the type of PD solution received on lipid parameters and CVE was weakened by inadequate statistical power. Future studies should consider comparing the effect of lipid-target vs non-target driven treatment strategies on CVEs in PD patients.

ACKNOWLEDGMENTS

This biomarker sub-study of the balANZ trial was funded by the Fresenius Medical Care Research Project Grant 2013.

DISCLOSURES

David Johnson is a consultant for Baxter Healthcare Pty Ltd and has previously received research funds from this company. He has also received speakers' honoraria and research grants from Fresenius Medical Care. He has previously been a consultant to Gambro Pty Ltd. He is an International Society for Peritoneal Dialysis Councillor and is a current recipient of a Queensland Government Health Research Fellowship. Yeoungjee Cho is a current recipient of an Australian Postgraduate Award and is a recipient of 2012 Jacquot Research Entry Scholarship. Carmel Hawley has received research grants from Baxter Healthcare Pty Ltd and Gambro Pty Ltd, and has been a consultant to Fresenius Medical Care. Jutta Passlick-Deetjen is a consultant to Fresenius Medical Care. Janine Büchel, Sonja Steppan, and Margaret Clarke are employees of Fresenius Medical Care.

REFERENCES

1. Johnson DW, Dent H, Hawley CM, McDonald SP, Rosman JB, Brown FG, *et al.* Association of dialysis modality and cardiovascular mortality in incident dialysis patients. *Clin J Am Soc Nephrol* 2009; 4:1620–8.
2. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia.

- Kidney Int* 2002; 62:1524–38.
3. Stenvinkel P, Alvestrand A. Inflammation in end-stage renal disease: sources, consequences, and therapy. *Semin Dial* 2002; 15:329–37.
 4. Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. *Am J Physiol Renal Physiol* 2006; 290:F262–72.
 5. Attman PO, Samuelsson O, Johansson AC, Moberly JB, Alaupovic P. Dialysis modalities and dyslipidemia. *Kidney Int Suppl* 2003:S110–2.
 6. Deighan CJ, Caslake MJ, McConnell M, Boulton-Jones JM, Packard CJ. Atherogenic lipoprotein phenotype in end-stage renal failure: Origin and extent of small dense low-density lipoprotein formation. *Am J Kidney Dis* 2000; 35:852–62.
 7. Jiang N, Qian J, Lin A, Lindholm B, Axelsson J, Yao Q. Initiation of glucose-based peritoneal dialysis is associated with increased prevalence of metabolic syndrome in non-diabetic patients with end-stage renal disease. *Blood Purif* 2008; 26:423–8.
 8. Bredie SJ, Bosch FH, Demacker PN, Stalenhoef AF, van Leusen R. Effects of peritoneal dialysis with an overnight icodextrin dwell on parameters of glucose and lipid metabolism. *Perit Dial Int* 2001; 21:275–81.
 9. Martikainen T, Teppo AM, Gronhagen-Riska C, Ekstrand A. Benefit of glucose-free dialysis solutions on glucose and lipid metabolism in peritoneal dialysis patients. *Blood Purif* 2005; 23:303–10.
 10. Babazono T, Nakamoto H, Kasai K, Kuriyama S, Sugimoto T, Nakayama M, et al. Effects of icodextrin on glycemic and lipid profiles in diabetic patients undergoing peritoneal dialysis. *Am J Nephrol* 2007; 27:409–15.
 11. Li PK, Culleton BF, Ariza A, Do JY, Johnson DW, Sanabria M, et al. Randomized, controlled trial of glucose-sparing peritoneal dialysis in diabetic patients. *J Am Soc Nephrol* 2013; 24:1889–900.
 12. Schmitt CP, von Heyl D, Rieger S, Arbeiter K, Bonzel KE, Fischbach M, et al. Reduced systemic advanced glycation end products in children receiving peritoneal dialysis with low glucose degradation product content. *Nephrol Dial Transplant* 2007; 22:2038–44.
 13. Zeier M, Schwenger V, Deppisch R, Haug U, Weigel K, Bahner U, et al. Glucose degradation products in PD fluids: do they disappear from the peritoneal cavity and enter the systemic circulation? *Kidney Int* 2003; 63:298–305.
 14. Galler A, Muller G, Schinzel R, Kratzsch J, Kiess W, Munch G. Impact of metabolic control and serum lipids on the concentration of advanced glycation end products in the serum of children and adolescents with type 1 diabetes, as determined by fluorescence spectroscopy and Nepsilon-(carboxymethyl)lysine ELISA. *Diabetes Care* 2003; 26:2609–15.
 15. Turk Z, Cavlovic-Naglic M, Turk N. Relationship of methylglyoxal-adduct biogenesis to LDL and triglyceride levels in diabetics. *Life Sci* 2011; 89:485–90.
 16. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, et al. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. *J Am Soc Nephrol* 2012; 23:1097–107.
 17. Johnson DW, Clarke M, Wilson V, Woods F, Brown FG. Rationale and design of the balANZ trial: a randomised controlled trial of low GDP, neutral pH versus standard peritoneal dialysis solution for the preservation of residual renal function. *BMC nephrol* 2010; 11:25.
 18. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, et al. The effect of low glucose degradation product, neutral pH versus standard peritoneal dialysis solutions on peritoneal membrane function: The balANZ trial. *Nephrol Dial Transplant* 2012; 27:4445–53.
 19. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, et al. The effects of biocompatible compared with standard peritoneal dialysis solutions on peritonitis microbiology, treatment, and outcomes: the balANZ trial. *Perit Dial Int* 2012; 32:497–506.
 20. Cho Y, Johnson DW, Vesey DA, Hawley CM, Pascoe EM, Clarke M, et al. Baseline serum interleukin-6 predicts cardiovascular events in incident peritoneal dialysis patients. *Perit Dial Int* 2014; In Press.
 21. Cho Y, Johnson DW, Vesey DA, Hawley CM, Pascoe EM, Clarke M, et al. Dialysate interleukin-6 predicts increasing peritoneal solute transport rate in incident peritoneal dialysis patients. *BMC Nephrol* 2014; 15:8.
 22. Quaschnig T, Krane V, Metzger T, Wanner C. Abnormalities in uremic lipoprotein metabolism and its impact on cardiovascular disease. *Am J Kidney Dis* 2001; 38:S14–9.
 23. Vaziri ND, Norris K. Lipid disorders and their relevance to outcomes in chronic kidney disease. *Blood Purif* 2011; 31:189–96.
 24. Little J, Phillips L, Russell L, Griffiths A, Russell GI, Davies SJ. Longitudinal lipid profiles on CAPD: their relationship to weight gain, comorbidity, and dialysis factors. *J Am Soc Nephrol* 1998; 9:1931–9.
 25. Holmes CJ, Shockley TR. Strategies to reduce glucose exposure in peritoneal dialysis patients. *Perit Dial Int* 2000; 20 Suppl 2:S37–41.
 26. Li Z, Fengxian H. Glucose concentration in the dialysate does not contribute to lipid profiles in patients undergoing capd. *Ren Fail* 2011; 33:124–30.
 27. Cho Y, Johnson DW, Badve SV, Craig JC, Strippoli GF, Wiggins K. Impact of neutral pH, low glucose degradation product peritoneal dialysis solution on clinical outcomes in peritoneal dialysis: a systematic review of randomized controlled trials. *Kidney Int* 2013; 84:969–79.
 28. Fischbach M, Issad B, Dubois V, Taamma R. The beneficial influence on the effectiveness of automated peritoneal dialysis of varying the dwell time (short/long) and fill volume (small/large): a randomized controlled trial. *Perit Dial Int* 2011; 31:450–8.
 29. Habib AN, Baird BC, Leyboldt JK, Cheung AK, Goldfarb-Rumyantzev AS. The association of lipid levels with mortality in patients on chronic peritoneal dialysis. *Nephrol Dial Transplant* 2006; 21:2881–92.