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Uric acid is associated with the rate of residual renal function decline in peritoneal dialysis patients

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Abstract

Background. Uric acid (UA) is known to play a pathogenic role in chronic kidney disease (CKD). However, its effect in end-stage renal disease (ESRD) has not yet been elucidated. We explored the prevalence of hyperuricaemia and the relationship between UA and residual renal function (RRF) in peritoneal dialysis (PD) patients.

Methods. The subjects of this study were 134 PD patients who started dialysis at the Yonsei University Health System between January 2000 and December 2005. Timed urine collections were performed within 1 month of PD commencement and at 6-month intervals thereafter. The slope of decline of RRF over time was calculated by linear regression analysis of serial urinary urea and creatinine clearances for each patient. Biochemical and clinical data at the time of initial urine collection were considered as baseline.

Results. At baseline, 32.8% of the PD patients had hyperuricaemia (UA $\geq$7.0 mg/dl). A significant majority of patients with hyperuricaemia were diabetic ($P = 0.02$). Hypertensive patients had a higher UA level ($P = 0.002$) compared to normotensive patients. The overall reduction rate of RRF in hyperuricaemic patients was significantly higher than in the normouricaemic group ($P = 0.001$). In the multiple linear regression analysis, hyperuricaemia and history of DM showed a significant negative correlation with the reduction rate of RRF after adjusting for demographic data, comorbid conditions, body mass index, baseline RRF and medications ($P = 0.001$).

Conclusions. Hyperuricaemia is common among PD patients and is significantly associated with the rate of decline of RRF.

Keywords: end stage renal disease; hypertension; peritoneal dialysis; residual renal function; uric acid

Introduction

There is an increasing body of evidence indicating that hyperuricaemia may have a role in the development of hypertension, kidney disease, cardiovascular events and mortality [1,2]. This has been well established in animal models that showed that uric acid (UA) was directly involved in the development and progression of hypertension and kidney disease, independent of intrarenal crystal formation [3,4]. The main mechanisms proposed by which UA causes these conditions involve the activation of the renin–angiotensin–aldosterone system [5], vascular smooth muscle cell proliferation [6] and impaired endothelial nitric oxide production [7].

Epidemiologic studies have showed that UA is an independent risk factor for the development and progression of

hypertension [8]. An elevated UA level was also associated with the progression of kidney disease in the normal population and in patients with hypertension, diabetes and chronic kidney disease (CKD) [9–12].

Since the kidney excretes approximately two-thirds of the UA produced daily, serum UA tends to rise in patients approaching ESRD. However, it is uncertain whether UA is a mediator of RRF decline in patients undergoing renal replacement therapies.

The aims of the present study were to explore the prevalence of hyperuricaemia in continuous ambulatory peritoneal dialysis patients (CAPD) and to investigate the relationship between hyperuricaemia and RRF loss.

Subjects and methods

Study population

Clinical and laboratory data were retrieved from the Yonsei PD Unit Database. The subjects of the study were 151 ESRD patients who started CAPD between January 2000 and December 2005 with serial urea kinetic studies, including measurements of RRF. Eight patients who were considered anuric, with a residual urine volume of <200 ml/day at the time of the initial urea kinetic study, were excluded. An additional nine patients who had received prior kidney transplants were excluded due to long-term use of immunosuppressive agents. Therefore, a total of 134 patients were included in this study. All patients were initially evaluated for RRF within 1 month of CAPD initiation. Patients were followed up for 24 months or until their measured urine volume was <200 ml/day.

RRF was calculated as an average of urea and creatinine clearance from a 24-h urine collection within 1 month of CAPD commencement, and thereafter at 6-month intervals [13]. Demographic and clinical data including sex, age, body mass index, primary renal disease, type of dialysate used (conventional or biocompatible solution), use of anti-hypertensive agents (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium channel blockers, beta blockers and diuretics) and allopurinol were collected as possible predictors of RRF decline. Different types of PD fluid (Baxter Healthcare, Deerfield, IL, USA; Fresenius Medical Care, Deutschland GmbH, Germany; and Gambro, Lund, Sweden) were used as conventional and biocompatible solutions. Peritonitis rate was recorded during the follow-up period. The following laboratory data obtained at the time of the initial urea kinetic study were considered as baseline: haematocrit, albumin, BUN, creatinine, CRP, UA, Kt/V urea, 4-h D/P creatinine and normalized protein catabolic rate (nPCR). Hypertension was defined as a positive history of hypertension or use of antihypertensive agents at the time of PD commencement. Hyperuricaemia was defined as a serum UA level ≥7.0 mg/dl.

Statistical analysis

Statistical analysis was performed using SPSS for Windows software, version 12.0 (SPSS Inc., Chicago, IL, USA). All data were expressed as mean ± SD. Due to the log-normally distributed value of RRF, the natural log values were used for analysis, and geometric means were calculated and reported with 95% confidence intervals (CI). We intended to predict the rate of change of RRF during the follow-up with variables, including the UA levels measured at baseline. The reduction rate of RRF over time was determined using least squares linear regression of RRF on time; this was calculated from serial urinary urea and creatinine clearances measured during the study period for each patient. The slope was expressed as the regression coefficient (ml/min/month/1.73 m^2). Two data points were used for calculating the regression coefficient in patients who had less than three measurements. It has been proposed that RRF declines exponentially, and therefore, the regression coefficient was calculated on both linear and logarithmic scales of RRF in order to assess the nature of RRF reduction [14]. Since the logarithmic scale of RRF showed a better linear correlation with the follow-up time, the reduction rate of RRF was calculated as the follow-up duration against RRF on a logarithmic scale. To compare differences between the hyperuricaemia and normal UA groups, Student's *t*-test and the χ^2 test were used. Pearson's correlation analysis was performed to estimate the correlation between the rate of reduction of RRF and other variables. Multiple linear regression analysis was used to identify significant determinants of the RRF reduction rate. In order to confirm the difference of RRF change over time between hyperuricaemia and normouricaemia groups, repeated measures ANCOVA analysis was used. When comparing time periods, the paired sample *t*-test was used for continuous variables and McNemar's test was used for categorical variables. For multiple regressions and repeated measures ANCOVA, adjustments were made for demographic factors, comorbid conditions, body mass index, baseline RRF and medications. A *P*-value of <0.05 was considered statistically significant.

Table 1. Demographic and baseline clinical data ($n = 134$)

Age (years)	53.8 ± 13.2
Gender (male/female)	59/75
History of diabetes mellitus	46 (34.3%)
Hypertension	112 (83.6%)
Body mass index (kg/m^2)	22.6 ± 2.8
Weekly Kt/V urea	2.6 ± 0.8
4-h D/P creatinine	1.1 ± 0.4
RRF (ml/min/1.73 m^2)	4.8 (4.4–5.6)
Primary kidney disease	
Diabetes	44 (32.8%)
Hypertension	34 (25.4%)
Glomerulonephritis	20 (14.9%)
Others	36 (26.9%)
BUN (mg/dl)	46.8 ± 16.3
Creatinine (mg/dl)	6.6 ± 2.2
Haematocrit (%)	33.7 ± 6.5
Albumin (mg/dl)	3.6 ± 0.6
CRP (mg/dl)	0.35 ± 0.55
Total cholesterol (mg/dl)	191.7 ± 40.0
UA (mg/dl)	6.6 ± 1.5
nPCR (g/kg/day)	1.1 ± 0.4
Medication	
ACE inhibitors or ARBs	78 (58.2%)
Calcium channel blockers	97 (72.3%)
Diuretics	70 (52.2%)
Beta blockers	68 (50.7%)
Allopurinol	15 (11.2%)
Dialysate	
Conventional	33 (24.6%)
Biocompatible solutions	101 (75.4%)
Peritonitis rate (times/patient-years)	0.2 ± 0.5

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; nPCR, normalized protein catabolic rate.
Data are expressed as mean ± SD or geometric mean (95% CI).

Results

Demographic characteristics and biochemical data

The clinical characteristics of the patients are shown in Table 1. The mean age was 53.8 ± 13.2 years, and 59 (44%) of the subjects were male. Diabetes was the most common cause of ESRD in this study (32.8%). The mean UA level was 6.6 ± 1.5 mg/dl with a range of 3.0–12.3 mg/dl. All patients were prescribed CAPD with a daily dialysate volume of 8 l.

Comparison between patients with hyperuricaemia and those with normal UA levels

At baseline, 32.8% of the patients had UA levels >7 mg/dl. When patients were divided into two groups on the basis of UA concentrations, there were no significant differences in age (54.9 ± 12.9 versus 51.1 ± 13.7 years, $P = 0.13$),

Table 2. Comparison of clinical and biochemical characteristics between hyperuricaemic patients and patients with normal UA levels

	UA <7 mg/dl ($n = 90$)	UA ≥7 mg/dl ($n = 44$)
Age (years)	54.9 ± 12.9	51.3 ± 13.7
Gender (male/female)	35/55	24/20
Diabetes	25 (27.8%)	21 (47.7%)*
Hypertension	69 (76.7%)	43 (97.7%)**
Body mass index (kg/m^2)	22.5 ± 2.8	22.8 ± 3.0
Weekly Kt/V urea	2.7 ± 0.8	2.5 ± 0.7
4-h D/P creatinine	0.77 ± 0.13	0.72 ± 0.14
RRF (ml/min/1.73 m^2)	5.0 (4.2–5.9)	5.0 (3.9–6.0)
Albumin (mg/dl)	3.5 ± 0.5	3.7 ± 0.8
CRP (mg/dl)	0.35 ± 0.59	0.36 ± 0.49
Total cholesterol (mg/dl)	195.3 ± 39.5	184.6 ± 40.3
nPCR (g/kg/day)	1.1 ± 0.3	1.1 ± 0.4
Allopurinol use	12 (17.1%)	3 (8.6%)
Peritonitis rate (times/patient-years)	0.2 ± 0.6	0.1 ± 0.4

RRF, residual renal function; nPCR, normalized protein catabolic rate. Data are expressed as mean ± SD or geometric mean (95% CI). *$P < 0.05$, **$P < 0.01$ versus UA <7 mg/dl group.

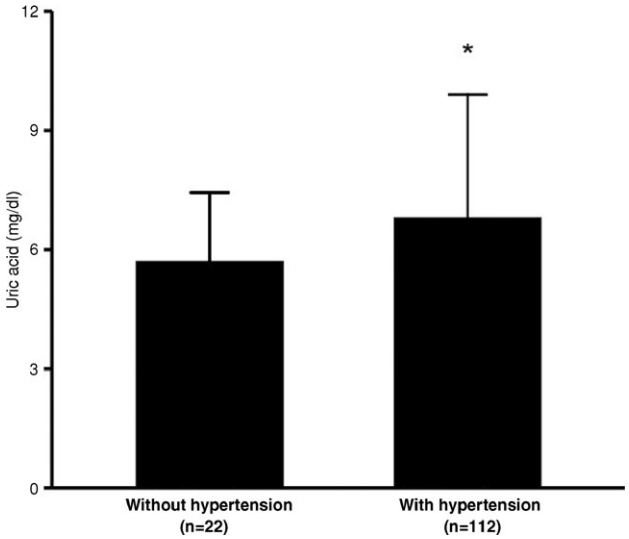

Fig. 1. Patients who did not have hypertension showed significantly lower mean UA levels compared to hypertensive patients. Each bar shows the mean and standard deviation of the mean. *$P < 0.05$ versus patients without hypertension.

body mass index (22.5 ± 2.8 versus 22.8 ± 3.0 kg/m^2, $P = 0.56$), proportion of males (38.9 versus 54.5%, $P = 0.09$), serum albumin (3.5 ± 0.5 versus 3.7 ± 0.8 mg/dl, $P = 0.07$), serum cholesterol (195.3 ± 39.5 versus 184.6 ± 40.3 mg/dl, $P = 0.15$) and serum CRP (0.35 ± 0.59 versus 0.36 ± 0.49 mg/dl, $P = 0.95$) between the two groups. In addition, nPCR (1.1 ± 0.3 versus 1.1 ± 0.4 g/kg/day, $P = 0.51$), baseline RRF (5.0; 95% CI: 4.2–5.9 versus 5.0; 95% CI: 3.9–6.0 ml/min/1.73 m^2, $P = 0.85$), D/P creatinine ratio (0.77 ± 0.13 versus 0.72 ± 0.14, $P = 0.05$), weekly Kt/V urea (2.7 ± 0.8 versus 2.5 ± 0.7, $P = 0.18$), the number of patients on allopurinol (17.1 versus 8.6%, $P = 0.38$) and peritonitis rate (0.2 ± 0.6 versus 0.1 ± 0.4 times/patient-years, $P = 0.65$) did not differ between the two groups. However, the proportion of patients with the history of diabetes was significantly higher in hyperuricaemic patients (27.8 versus 47.7%, $P = 0.02$) (Table 2). There was no correlation between baseline RRF and UA level ($r = -0.13$, $P = 0.21$).

Consistency of serum UA levels

The prevalence of hyperuricaemia did not change at the 12-month follow-up (32.8 versus 33.3%, $P = 1.0$), and the mean UA values also remained unchanged (6.64 ± 1.45 versus 6.63 ± 1.50 mg/dl, $P = 0.97$). There was a positive and statistically significant correlation between baseline serum UA levels and mean serum UA levels ($r = 0.80$, $P < 0.001$).

UA and hypertension

Hypertension was observed in 83.6% of the patients starting PD. The proportion of patients with hypertension was significantly higher in hyperuricaemic patients (76.7 versus 97.7%, $P < 0.001$) (Table 2). In addition, the UA level was higher in PD patients with hypertension compared to those without hypertension (6.8 ± 1.6 versus 5.7 ± 0.9 mg/dl, $P = 0.002$) (Figure 1).

UA and reduction rate of RRF

All patients had a minimum of two timed urine collections to measure RRF (90.3% had at least three collections performed). A significant correlation was found between the follow-up duration and the exponential decline of RRF, with a correlation coefficient (r) of 0.469 ($P < 0.001$). In contrast, when RRF was represented on a linear scale, the decline of RRF and the follow-up duration showed a weaker linear correlation ($r = 0.328$, $P < 0.001$). Therefore, the follow-up duration and RRF were better correlated logarithmically.

During the study period, the overall RRF declined more rapidly in hyperuricaemic patients than in the normouricaemic group (−0.20 ± 0.17 versus −0.08 ± 0.20 ml/min/month/1.73 m^2, $P = 0.001$).

Hyperuricaemia had an inverse relation with the reduction rate of RRF (β = −0.35, $P = 0.001$). A negative relationship with the reduction rate of RRF was also found in males (β = −0.21, $P = 0.02$) and diabetics (β = −0.36, $P < 0.001$). However, there was no significant correlation between the reduction rate of RRF and body mass index (β = −0.16, $P = 0.07$), diuretic use (β = −0.04, $P = 0.67$), use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (β = −0.03, $P = 0.76$) or peritonitis rate (β = −0.15, $P = 0.08$). The use of biocompatible solutions also showed no association with the rate of RRF decline (β = 0.01, $P = 0.91$). Multivariate linear regression analysis showed that the history of diabetes (β = −0.26, $P = 0.02$) and hyperuricaemia at baseline (β = −0.36, $P = 0.001$) were associated with the reduction rate of RRF independent of age, gender, history of diabetes and hypertension, body mass index, baseline RRF and medications (Table 3). When further analysis was done using

Table 3. Multiple linear regression analysis between the reduction rate of RRF and other variables

	Univariate		Multivariate	
Variables	β	*P*-value	β	*P*-value
Hyperuricaemia (uric acid ≥7 mg/dl)	−0.35	0.001	−0.36	0.001
Age (years)	0.08	0.38	0.10	0.24
Male	−0.21	0.02	−0.06	0.46
History of DM	−0.36	<0.001	−0.25	0.001
History of hypertension	−0.05	0.58	0.03	0.76
Body mass index (kg/m^2)	−0.16	0.07	−0.11	0.20
Baseline RRF (ml/min/1.73 m^2)	−0.27	0.003	−0.21	0.01
nPCR (g/kg/day)	−0.03	0.70	0.05	0.53
Use of biocompatible solutions	0.01	0.91	0.04	0.60
Peritonitis rate (times/patient-years)	−0.15	0.08	−0.04	0.59
Diuretic use	−0.04	0.67	0.02	0.78
Allopurinol use	−0.01	0.87	−0.01	0.93

RRF, residual renal function; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

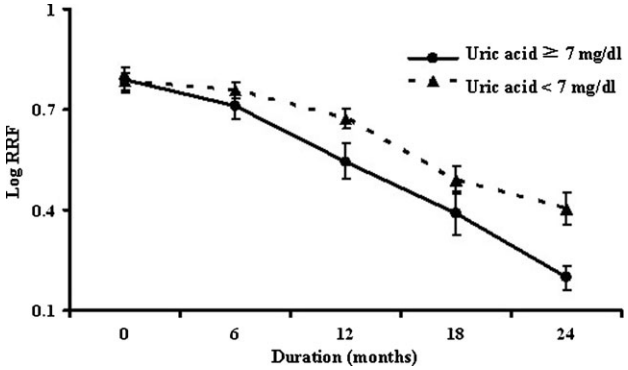

Fig. 2. Changes in log RRF over time between hyperuricaemic (uric acid ≥7 mg/dl) and patients with normal uric acid levels (uric acid <7 mg/dl). Means and error bars are presented for each visit. RRF, residual renal function.

repeated measures ANCOVA, a significant interaction effect was found between time and UA groups ($F_{(4.0, 160.0)} = 2.77$, $P = 0.03$). Additionally, the between-subjects effect comparing the hyperuricaemic and normouricaemic groups was significant ($F_{(1, 40)} = 5.88$, $P = 0.02$) with adjustment for age, sex, DM, hypertension, BMI, baseline RRF and medications, which suggests that changes in log RRF were independently influenced by UA levels. The plot in Figure 2 shows almost equal levels of RRF at baseline, but at follow-up higher RRF levels were found in patients with lower UA at baseline.

Discussion

In the present study, we found that hyperuricaemia is common among ESRD patients on CAPD, occurring in ∼30% of the population. Additionally, hypertensive patients had higher UA levels, suggesting a close relationship between UA and hypertension. An important finding of our study is that baseline UA level was independently associated with the rate of RRF decline, even after adjustment for renal function at baseline.

Due to the progressive loss of glomerular filtration, ESRD patients have lower renal UA clearance and higher serum UA levels. In a study by Ifudu *et al*. [15], the mean serum UA level in maintenance haemodialysis patients was 7.6 ± 1.8 mg/dl (7.6 ± 1.8 mg/dl in men and 7.5 ± 1.6 mg/dl in women). In our study, the mean UA level was lower, and although there was no statistical significance, men tended to have a higher UA level than women (6.8 ± 1.4 versus 6.5 ± 1.6 mg/dl, $P = 0.15$). The lower UA levels in our study may have been due to the fact that only ESRD patients with significant RRF were recruited. However, UA levels in our population were still higher than in the general population [16].

Serum UA has been assumed to be involved in the development of hypertension [8]. Even though hypertension is a common feature in ESRD patients, the role of UA in the development and progression of hypertension in this population is not well understood. We have shown that hypertensive patients on PD have higher UA levels. Although a causal relationship between hypertension and UA was not shown, our preliminary data reveal that there may be an association between hypertension and UA in the ESRD population.

UA has been proposed to be associated with renal disease. UA-induced preglomerular arterial disease, renal inflammation and activation of RAS and COX-2 have been demonstrated as potential mechanisms by which UA acts on the progression of renal disease [5,17,18]. Several clinical studies have confirmed that UA is an independent risk factor for the development of renal disease in the normal population as well as in patients with previous kidney disease, such as IgA nephropathy [9,11]. Additionally, in the renal transplant recipient population, a relationship between UA and graft dysfunction has been demonstrated [19]. In a recent community-based prospective study of 13 338 participants, UA level was described to be an independent risk factor for the development of kidney disease and mortality [20]. However, to date very little information is available in the literature on the role of UA in patients on dialysis.

The present data show that during the initial 2 years of PD commencement, UA level was independently associated with the rate of RRF decline, even after adjusting for baseline RRF. This suggests that UA may be a risk factor for RRF decline among ESRD patients on PD.

Several studies have found that RRF is an essential marker of patient and technique survival during PD [21–25]. A cohort study of 1446 PD patients showed that each 10 l/week/1.73 m^2 increase in the urinary component of weekly creatinine clearance was associated with a 40% decreased risk of death [26]. The ADEMEX study and re-analysis of the CANUSA study have clearly demonstrated that the predictive power for mortality in patients on PD was attributed to RRF [21,27]. However, strategies for preserving RRF are limited. Based on the present results, lowering UA in PD patients could benefit RRF preservation. However, the use of allopurinol had no effect on RRF preservation in this study. The fact that there was no difference in the proportion of patients prescribed for allopurinol

between the hyperuricaemic and normal UA groups implies that the medication had not been properly used to lower UA levels. In order to prove the causal relationship between UA and RRF, further prospective studies should be performed that examine the effect of lowering UA on RRF.

In verifying the correlation between UA with the rate of RRF decline, a logarithmic value of RRF was used. RRF showed a better linear correlation with the follow-up duration when represented on a logarithmic scale, which was in concordance with previous reports [14,28].

Not surprisingly, we found that the history of diabetes was negatively associated with the rate of RRF decline. Diabetes, as well as hypertension, has been recognized as a risk for renal function loss in chronic renal failure patients. The presence of diabetes in predicting RRF loss, particularly in the PD population, has also been mentioned in previous epidemiologic studies [29,30]. There have been confounding reports on the effect of biocompatible solutions on the preservation of RRF [31,32]. In our study, there were no differences in baseline characteristics between patients using conventional and biocompatible solutions (data not shown). Nevertheless, we found no association between the use of biocompatible solutions and the RRF reduction rate.

There are a number of limitations to this study. This is an observational and relatively small study without intervention. Therefore, it is quite difficult to determine the current observation as a cause or consequence. Further randomized controlled trials intentionally lowering UA levels should be needed to clarify this issue. In addition, single measures of UA levels could have reflected acute changes in UA that might have been induced by diet or exercise. However, the mean UA level and proportion of hyperuricaemic patients did not change during a 1-year period, indicating that serum UA levels were consistent during the study period after PD commencement. Despite these limitations, it should be noted that UA was independently associated with the rate of RRF decline.

In conclusion, this study shows that hyperuricaemia is a common finding in CAPD patients, and the rate of RRF loss was significantly related to baseline UA level in CAPD patients. These results suggest that there is an association between UA level and the decline rate of RRF in patients on PD.

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Conflict of interest statement. None declared.

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Assessment of cardiovascular risk in paediatric peritoneal dialysis patients: a Turkish Pediatric Peritoneal Dialysis Study Group (TUPEPD) report

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Abstract

Methods. We aimed to clarify arteriosclerotic risk and to document possible relationships between cardiovascular risk factors and echocardiographic parameters in paediatric peritoneal dialysis (PD) patients. M-mode/Doppler/tissue Doppler echocardiographic studies and lipid/lipoproteins, homocysteine, high-sensitivity C-reactive protein (HS-CRP) levels and carotid intima–media thickness (CIMT) were determined in 59 patients (age: 14.2 ± 4.5 years) and in 36 healthy subjects.

Results. Structural and functional cardiac abnormalities were observed in patients on maintenance dialysis. Increased left ventricular mass index (LVMI, $P = 0.000$), relative wall thickness ($P = 0.000$), myocardial performance index (MPI, $P = 0.000$) were documented in the patients. Lipoprotein (a) ($P = 0.000$), homocysteine ($P = 0.001$), HS-CRP ($P = 0.000$) and CIMT ($P = 0.000$) were significantly elevated in the patients. Left ventricular hypertrophy (LVH) was prevalent in 68% of the patients. Patients with LVH had higher levels of HS-CRP ($P = 0.001$) and CIMT ($P = 0.028$) than those without LVH. Haemoglobin was an independent predictor of LVMI (β: −8.9, $P = 0.001$), while residual diuresis and CIMT were independent predictors of diastolic dysfunction (β: −0.45, $P = 0.034$ and β: 5.90, $P = 0.008$, respectively). Albumin (β: −0.72, $P = 0.018$) and Kt/V urea (β: −0.48, $P = 0.012$) were significant predictors of CIMT. There were positive correlations between LVMI and CIMT. HS-CRP was positively correlated with LVMI as well as CIMT.

Conclusions. Elevated levels of atherosclerotic/inflammatory risk factors, low haemoglobin levels and loss of residual renal function and their negative effects on heart are of remarkable importance in paediatric patients on maintenance peritoneal dialysis. Achieving recommended targets for haemoglobin, blood pressure and Kt/V urea, preserving residual renal function as well as