Original article

Correlation of Residual Diuresis with MIS Score and Nutritional Status in Peritoneal Dialysis Patients: A Croatian Nationwide Study

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Abstract

Introduction. Residual diuresis (RD) is an important predictor of mortality and cardiovascular (CV) deaths in peritoneal dialysis (PD) patients, and contributes more to overall survival compared to PD clearance. In this study we investigated the correlation between RD and CV outcomes in PD patients.

Methods. A total of 190 PD patients from 13 dialysis centers, a national representation, were included in this analysis. Biomarkers of anemia, nutritional status [malnutrition inflammation score (MIS), subjective global assessment (SGA), serum albumin, anthropometric measurements including body mass index (BMI)], dialysis dose (Kt/V) and laboratory measurements were determined. RD was estimated using the volume of daily urine.

Results. There were 78(41.05 %) females and 112 (58.95 %) males; aged 57.35 ± 14.41 years, on PD for 24.96 ± 24.43 months. Fifty-six patients had diabetes type II (44 as primary kidney disease). The mean RD was 1170 ± 673.6 ml (range 0-3000 mL). Statistically significant correlations between RD and BMI, hip circumference, time on PD, Kt/V, MIS, SGA, erythrocytes (E), Hemoglobin (Hb), PTH, and serum albumin were observed.

Conclusions. We demonstrated a significant correlation between RD and MIS score, SGA, anthropometry and albumin. Every effort should be invested to maintain RD for as long as possible to achieve optimal treatment results and to decrease CV mortality in PD population.

Key words: peritoneal dialysis, residual diuresis, anemia, nutritional status, CKD-MBD, MIS score

Introduction

Cardiovascular (CV) related diseases are the leading causes of death in dialysis patients; CV issues account for more than 40% of deaths in the dialysis population [1]. Residual diuresis (RD) is an important predictor of both overall and CV mortality in peritoneal dialysis (PD)

patients. Maiorca *et al.* were the first group to report a 50% reduction in mortality in peritoneal dialysis (PD) patients who maintained some RD [2]. Diaz-Buxo *et al.* demonstrated strong association between residual renal creatinine clearance and PD patient survival, whereas peritoneal clearance did not affect mortality [3]. These findings have been supported by many additional studies in various countries which have all highlighted the importance of maintaining RD to reduce mortality in PD patients [4-10]. Additional benefits for patients with preserved RD were reported, including improved quality of life and reduced systemic inflammation [11,12]; a reduction in systemic inflammation may reduce the incidence of protein-energy wasting.

Residual diuresis is important for small solute clearance, removal of middle molecular uremic toxins, maintenance of fluid balance, as well as for phosphorus control, the role of the kidney in nutrient homeostasis, vit. D activation, erythropoietin production, minerals, carnitine production, etc. This would set the story as to why one is measuring nutritional markers and status. The decline of RD also contributes significantly to anemia, inflammation, and malnutrition in patients on dialysis, and correlates with valvular calcification and cardiac hypertrophy [13]. However, a decline in RD is inevitable with time on dialysis, demanding an increase in the reliance on PD clearance to compensate for the loss in RD. Because the kidney has a key role in nutrient homeostasis, in this study we investigated the correlations between RD and nutritional status, and other parameters associated with CV outcomes in Croatian PD patients.

Materials and methods

The PD registry of the Croatian society for nephrology, dialysis and transplantation was utilized to collect data from 190 Croatian PD patients, who are being treated in 13 dialysis centers countrywide, for inclusion into this analysis. This study was approved by the Ethics committee of the University hospital center in Zagreb. All patients treated with PD in Croatia were included in the PD registry, and in this investigation. Biomarkers of anemia, nutritional status [malnutrition inflammation score (MIS), subjective global assessment (SGA) score, serum albumin, body mass index (BMI)], anthropometric measurements (skinfold thickness measured at the triceps region, hip and waist circumference) and laboratory measurements (calcium, potassium, phosphorus) were determined. RD, or residual diuresis, was estimated using volume of daily urine. Hypertension was defined as the need for antihypertensive drugs other than a diuretic for the maintenance of blood pressure below 140/90 mmHg. Adequacy of dialysis was determined by the total weekly urea clearance (Kt/V). Transport characteristics were determined by the PET test.

Statistical analysis was performed using commercially available software; Statistic 6.1 StatSoft [StatSoft, Inc. (Dell Software), Tulsa, OK, USA]. The relationship between any two parameters was tested by regression analysis. Statistical differences between parameter values were tested by either the t-test or χ -square test as appropriately. A p value of less than 0.05 was considered statistically significant.

Results

Our study cohort had a mean age of 57.35±14.41 years

Table 1. Patients' characteristics

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Characteristic	Value		
Females (No. (%))	78(41.05)		
Males(No. (%))	112(58.95)		
Age (years; mean±SD)	57.35±14.41		
Dialysis vintage (months; mean±SD)	24.96±24.43		
Primary kidney disease (No. (%))			
Renovascular	46(24.2)		
Diabetes mellitus	44(23.15)		
Glomerulonephritis	55(28.95)		
ADPKD	17(8.95)		
Other	28(14.75)		
Smokers (No. (%))	41(21.58)		
Hypertension (No. (%))	177(93.8)		

with mean PD duration of 24.96 ± 24.43 months at study enrolment. Of the 190 patients, diabetes type II was the primary cause of kidney disease in 44 patients. An additional 12 patients developed diabetes after the study period started. Patients' characteristics are presented in Table 1. The mean RD was 1170 ± 674 ml (range 0-3000 ml). Transport characteristics were as follows: 55(28.95%) patients were considered high average, 63(33.15%) patients were considered low average, 19(10%) patients were considered low and 26(13.7%) were considered high transporters. Data for 27 patients was missing. The mean weekly total Kt/V was 2.42 (range 1.42-4.25). In our regression analysis, RD significantly correlated with Kt/V (r= 0.4374, p<0.001).

Statistically significant correlations between RD and numerous potential CV diseases risk factors were found (Table 2). Namely, positive correlation was observed for BMI, hip circumference, Kt/V, E, Hb and serum albumin, with negative correlation of RD with iPTH, MIS, SGA and dialysis vintage was recorded.

Table 2. Statistically significant correlations between RRF and CV disease-related parameters in PD patients (Pearson's correlation coefficient, one-tailed significance level). MIS - malnutrition inflammation score, SGA - subjective global assessment, E - erythrocytes, Hb - hemoglobin, iPTH - intact parathyroide hormone

Variable	Correlation coeficient	Р
BMI (kg/m^2)	0.3341	0.000003
Hip circumference (cm)	0.2571	0.0062
PD vintage (months)	-0.3927	0.00000003
Kt/V	0.4374	0.000000007
MIS	-0.4767	0.0000005
SGA	-0.3048	0.0087
Е	0.1524	0.0384
Hb	0.1614	0.0282
iPTH (pmol/L)	-0.1816	0.0174
Serum albumin (g/L)	0.2263	0.0022



Fig. 1. Correlation between serum albumin and residual diuresis. Patients with lower residual diuresis had lower serum albumin

Residual diuresis correlated with nutritional parameters (albumin, MIS, SGA, BMI and hip circumference) (Table 2). Other anthropometric parameters (neck or brachial circumference) had no significant correlation with RD. Serum albumin was reduced significantly in patients with declining residual diuresis (Figure 1).



Fig. 2. Patients with serum albumins <38 g/L had significantly lower residual diuresis compared to patients with serum albumins ≥ 38 g/L

Patients with serum albumin \geq 38 g/L had significantly higher residual diuresis when compared to those with serum albumin <38 g/L (Figure 2).

Additionally, low residual diuresis had a negative impact on BMI (Figure 3), and patients with BMI<23 kg/m² had significantly lower RD (residual diuresis) than patients with BMI \ge 23 kg/m² (Figure 4).



Fig. 3. Correlation between BMI (kg/m²) and residual diuresis. Patients with lower residual diuresis had lower BMI



Fig. 4. Patients with BMI ${\geq}23$ kg/m² had significantly higher residual diuresis than patients with BMI ${<}23$ kg/m²



Fig. 5. Correlation between MIS score (kg/m²) and residual diuresis. Patients with lower residual diuresis had higher MIS score

MIS was available for 101 patients. Both MIS (Figure 5) and SGA (N=48) (data not shown) had significant negative correlation with RD in our cohort of patients. We further investigated the correlation between anemia

and RD. Erythropoietin (EPO) was used for treatment of anemia in 127 patients. Patients with a higher RD had a higher serum hemoglobin level (Figure 6), and required less erythropoietin stimulating agents (ESA) (Figure 7).



Fig. 6. Correlation of serum hemoglobin with residual diuresis. Patients with higher residual diuresis had higher serum hemoglobin







Fig. 8. Correlation of iPTH and residual diuresis. Patients with lower residual diuresis had higher iPTH

Additionaly, RD significantly correlated with iPTH level (Figure 8).

Serum iPTH correlated with age (r=-0.1995, p=0.0081), use of EPO (ANOVA F=2.9924, p=0.032), weekly dose of EPO (r=0.1934, p=0.0103), and use of bicarbonates for treatment of metabolic acidosis (t=-2.32614, p=0.021242). Phosphorus level had no significant correlation with RD, but significantly correlated with Kt/V (r=-0.2192, p=0.0053). There was no correlation of serum calcium with other parameters.

Based on our definition of hypertension (need for antihypertensive drugs other than a diuretic for the maintenance of blood pressure below 140/90 mmHg) 93.8 % of patients were hypertensive, and required at least one antihypertensive drug in addition to a diuretic. A trend toward lower blood pressure and arterial pulse pressure was observed in patients with higher RD. However, RD was not significantly correlated with either systolic or diastolic blood pressure. Patients with diabetes needed less antihypertensive drugs than non-diabetic patients (t -2.12403, p =0.035018).

Table 3. Statistically significant correlations between use of icodextrin and other parameters in PD patients (t-test or χ -square, as appropriate). EPO - erythropojetin, Hb - hemoglobin

square, as appropriate). Er O - er yunopoleun, rio - nemogiooni			
Parameter	Correlation	Р	
Episodes of peritonitis (No)	2.75086	0.006625	
Antihypertensive drugs (No)	1.98222	0.049135	
Use of EPO	19.58887	0.00021	
Weekly dose EPO	2.13973	0.033855	
Transport type (high)	25.41760	0.00001	
Nutritive support (yes)	6.067899	0.01377	
Hb (g/L)	-2.86562	0.004708	
Plattelet (No.)	2.27902	0.023971	
Calcium (mmol/L)	-2.46832	0.014607	
Phosphorus (mmol/L)	2.16569	0.031788	
Creatinine (µmol/L)	2.30323	0.022522	
Albumin (g/L)	-3.02474	0.002900	
Residual diuresis	-2.28732	0.023463	

Forty-one patients (21.58%) were smokers, however, there was no correlation between smoking status and RD. Mean total cholesterol was 5.28 ± 4.75 mmol/L, LDL 3.03 ± 1.12 mmol/L, and HDL 1.20 ± 0.36 mmol/L, with triacylglycerides 2.07 ± 1.19 mmol/L. There was no correla-

tion between total cholesterol, LDL, HDL or triglycerides and RD.

Over half (53%) the subjects were prescribed PD using once daily long dwell exchange, with icodextrin as the principal osmotic agent. Use of icodextrin significantly correlated with various clinically relevant parameters (Table 3).Finally, we investigated the influence of anuria on observed parameters. Twenty-two patients (11.57%) were anuric with daily urine output <200 ml. The median age of anuric patients was 57 ± 19 years, with PD duration 52 ± 39.67 months vs. 21.5 ± 19.25 months in patients with preserved RD (p=0.000000022). Anuric patients had lower Kt/V (1.88 ± 0.31 vs. 2.47 ± 0.37 , p=0.0034), lower serum albumins (34.47 ± 3.52 g/L vs. 38.07 ± 4.17 g/L, p=0.000266) (Figure 9), lower BMI (23.65 ± 2.43 kg/m² vs. 26.86 ± 6.35 kg/m², p=0.041), and lower serum calcium (2.16 ± 0.18 vs. $2,26\pm0.17$, p=0,014), but higher CRP (9.28 ± 7.98 mg/L vs. 5.19 ± 7.2 mg/L, p=0.015) and MIS score (7.38 ± 3.46 vs. 3.31 ± 2.82 , p=0.00022) than patients with RD, respectively. Finally, anuric patients had a significantly higher iPTH (65.64 ± 110.96 pmol/L vs. 32.7 pmol/L, p=0.0012).



Fig. 9. Serum albumin and residual renal function. Anuric patients had significantly lower serum albumin compared to patients with residual diuresis (RRF)

Discussion

In the present cross-sectional study, we investigated the association between residual diuresis and nutritional status and other potential cardiovascular risk factors in Croatian PD population. All patients on renal replacement therapy with PD in Croatia, from 13 different dialysis centers, were included in this study. This is the first study, to our knowledge, that provides a national overview of the nutritional status of current PD patients.

The mean PD duration was 24.96±24.43 months. A relatively short PD duration is a consequence of the extremely well-developed renal transplant program in Croatia with an average waiting time of less than two years, what causes drop-out of many PD patients very soon after starting with the method.

Hypoalbuminemia is a well-known adverse factor for progressive left ventricular hypertrophy, left ventricular dilation and cardiac failure in dialysis patients, thus contributing to CV mortality in the dialysis population [14-16]. Previous studies have confirmed the importance of urea clearance and nutritional status in predicting the survival of dialysis patients [17-21]. In our cohort, residual diuresis correlated with nutritional parameters (serum albumin, MIS, SGA, BMI and hip circumference), but interestingly, not with waist or brachial circumference. Additionally, anuric patients had lower dialysis adequacy (Kt/V), nutritional parameters (serum albumins, BMI), and higher CRP and MIS, thus having additionally increased risk for CV disease [22], and PEW.

Our results suggest that patients with better preserved RD were significantly less anemic despite having a lower requirement for EPO, which may decrease the risk for developing left ventricular hypertrophy [23], as well as other negative cardiovascular events [24].

Patients with preserved residual diuresis had a lower iPTH; without impacting serum phosphorus in Croatian PD patients. Disordered mineral bone metabolism was not a significant adverse factor for loss of residual diuresis in previous studies [25]. Lopez-Menchero *et al.* analyzed the impact of RD on mineral bone metabolism in 37 PD patients and showed that RD was significantly correlated with serum phosphate levels (r(2)=0.19; beta=-0.594), but not with calcium or PTH [26]. Dong *et al.* found a low prevalence of hyperphosphatemia in those with RD and anuric patients [27]. The main difference between our results and previous studies may be due to the widespread use of phosphate binders, espe-

cially sevelamer, in those studies. In the Croatian PD population, there is a flexible approach to sevelamer use; through our phosphate education program less phosphate binders are used overall as it depends on the phosphate content in foods.

Hypertension is the primary contributory factor to cardiovascular mortality in the dialysis population. There was no correlation between arterial hypertension, smoking status or dyslipidemia with RD in Croatian PD population. Menon et al. have shown that residual urine output (P<0.001) was an independent risk factor for poor BP control [28]. In a meta-analysis, long-term use (≥12 months) of ACEis or ARBs showed additional benefits of preserving residual kidney function in CAPD patients, with no significant difference on residual kidney function preservation between ARBs and ACEis. Zhang et al. concluded that, there is currently insufficient evidence to support the use of an ACEi or an ARB as first line antihypertensive therapy in PD patients because of small number of RCTs with small number of participants [29]. This suggests that the major problem with hypertension control in anuric patients is volume control in peritoneal dialysis [30]. Use of bioimpendance for estimation of potential volume overload might explain lack of correlation between arterial hypertension and RD in our population.

There is evidence of an association between peritonitis episodes and loss of RD [31,32]. This was not found in our population. However, we found a correlation between the number of peritonitis episodes and use of icodextrin, demonstrating the loss of ultrafiltration capacity. Patients using icodextrin were found to have much greater net ultrafiltration (UF) and a lower incidence of negative net UF compared to solutions with different glucose concentrations. A recent Cochrane meta-analysis concluded that whereas icodextrin increased ultrafiltration compared with a standard 2.27 g/L glucose exchange, it had no effect on RD [33]. In the present study, we showed correlations between the use of icodextrin and numerous cardiovascular risk factors (Table 3) such as anemia, hyperphosphatemia and hypoalbuminemia, but not with MIS or SGA.

Many studies have investigated the role of residual diuresis compared with peritoneal clearance and factors associated with its preservation [9-11,34]. All these studies have come to the same conclusion; peritoneal clearance may not substitute the loss of residual diuresis [9,10]. Thus, every effort should be made, by health care professionals, to slow down the decrease in residual diuresis. Results from this study suggest that in order to decrease the rate of RD loss in patients treated with PD, the following has to be done: strict control of blood pressure, avoidance of nephrotoxic agents, optimal control of blood glucose in patients with diabetes mellitus and the use of ACE inhibitors or A-II receptor antagonists, both in patients with diabetic nephropathy and in patients with other causes of kidney failure. Additionally, loop diuretics should be used to increase salt and water excretion, urinary tract infections should be treated, metabolic bone disease should be prevented and treated, and finally, nutritional status should be maintained [13]. Thus, an integrative approach, individualized for each patient's characteristics may decrease the rate of RD loss in PD population, keeping in mind the increased risk for development of cardiovascular diseases in patients with end-stage renal disease [35-37].

MIS is a valuable tool for identifying patients with protein energy wasting [38-40]. The Croatian society for nephrology, dialysis and transplantation has included MIS in the routine screening of dialysis patients. However, MIS is rarely used in clinical practice, and data about its application in peritoneal dialysis patients is scarce [41,42]). To the best of our knowledge, in the present study, for the first time, we demonstrated a correlation between MIS and residual diuresis thus highlighting its additional importance in clinical practice, and the importance of preventing and treating PEW.

The limitation of our study, in addition to the fact that it is an observational study and does not show cause and effect, is our estimation of residual diuresis by volume of residual urine. Clinically, RD is assessed by evaluating 24-h urine clearances and determining the arithmetic average of creatinine clearance (Cl_c) and urea clearance (Cl_u) [43,44]. However, even contemporary methods are all unreliable and either underestimate or overestimate GFR in patients on PD [45,46]. However, this study represents a nation and not one particular clinic, which is its advantage. It provides insight into the clinical practice and current status of peritoneal dialysis in the country, which may influence standard of care and health policy in Croatia.

Conclusion

In conclusion, our study demonstrated a significant correlation between RD (measured as residual diuresis) with MIS, nutritional status and other cardiovascular risk factors in PD patients. By preserving RD and maintaining nutritional status we may possibly decrease cardiovascular mortality which is the leading cause of death in dialysis population.

Practical application: Our results for the first time emphasize the role of MIS in follow-up of patients treated with peritoneal dialysis, and correlates MIS with residual diuresis. Every effort should be invested to preserve residual diuresis, and to lower MIS score.

Conflict of interest statement. None declared.

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