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High rates of protein intake are associated with an accelerated rate of decline of residual kidney function in incident peritoneal dialysis patients

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Abstract

Background
Preservation of residual kidney function (RKF) is a relevant objective in peritoneal dialysis (PD) patients. The influence of dietary protein intake (PI) on this variable has not been adequately investigated.

Methods
Following an observational design, we studied 336 patients incident on PD, with a minimum follow-up of 6 months. The main study variable was the mean PI [normalized rate of protein nitrogen appearance (nPNA)] during the first 4 months on PD. The main outcome variables were the absolute rate of decline of RKF and the proportion of patients presenting a >50% decay of their RKF during the first year of follow-up. We applied univariate and multivariate strategies of analysis, taking into consideration the main control variables bearing a correlation with nPNA and/or RKF.

Results
Mean nPNA (first 4 months) was 1.23 ± 0.33 g/kg/day, while the overall rate of decline of RKF was -0.13 ± 0.29 mL/min/month; 69 patients (25.1%) had lost >50% of their initial RKF by the end of the first year. Univariate analysis disclosed consistent associations between the main study variable on one hand and baseline RKF ($r = 0.32$, $P < 0.0005$) and its rate of decline ($r = -0.23$, $P < 0.0005$) on the other. The latter two variables were also significantly correlated ($r = -0.36$, $P < 0.0005$). Multivariate analysis identified mean nPNA as an independent predictor of the rate of decline of RKF [odds ratio 1.09 per 0.10 g/kg/day, 95% confidence interval (CI) 0.99–1.19, $P = 0.058$] and, in particular, of the probability of losing >50% of the baseline RKF during the first year of treatment (odds ratio 1.15 per 0.10 g/kg/day, 95% CI 1.04–1.27, $P = 0.006$).

Conclusion
Higher rates of PI during the first months of therapy are associated with a faster decline of RKF among patients incident on PD. Our results underline the convenience of keeping an adequate balance between sufficient protein ingestion, to prevent malnutrition and wasting, and sensible restriction in stable, adequately nourished individuals with rates of intake in the higher range or above-recommended allowances.

Keywords
Malnutrition, nPNA, peritoneal dialysis, protein intake, residual kidney function
Topic
Peritoneal dialysis, cachexia, renal function, dietary proteins, follow-up, malnutrition, nitrogen, ingestion, outcome variable, univariate analysis

Introduction

Malnutrition represents a feared complication of chronic kidney disease (CKD), due to its significant prevalence and detrimental impact on the outcome of affected individuals. Current recommendations for the management of patients at different stages of CKD pay particular attention to the prevention and treatment of this complication [1].

Maintaining an adequate protein intake (PI) is an essential step in the management of patients with CKD. This measure permits prevention of malnutrition, and may help to mitigate the negative effects of protein-energy wasting, a multifactorial complication frequently present in these subjects [2, 3]. However, it has long been known that dietary protein may also exert some negative effects on CKD patients, including an increase in uraemic toxicity and a potentially faster decline of residual kidney function (RKF) [4, 5]. As a consequence, dietary recommendations have been traditionally different for patients at different stages of CKD. For those not yet on dialysis therapy (in whom prevention of progression of CKD is a priority), moderate restriction of PI is endorsed by a majority of studies [6–9]. On the contrary, a more liberal PI is usually allowed to patients undergoing renal replacement therapy [10, 11], in the belief that dialysis is a catabolic condition demanding a reinforced nutritional support, that protein-induced uraemic toxicity can be controlled with an adequate dosing of dialysis and that RKF may not be as relevant as in patients on conservative treatment. However, the latter view has been challenged during the last two decades, for at least two reasons. First, a variable proportion of dialysis patients maintain relatively high rates of PI, often exceeding current recommendations [12, 13]. The balance between the benefits and disadvantages of 'protein indulgence' in this setting is largely undetermined. Secondly, nephrologists have become progressively aware of the clinical advantages of preserving RKF in patients treated with either haemodialysis [14] or peritoneal dialysis (PD) [15]. These considerations raise the hypothesis that high rates of PI may not be particularly beneficial for dialysis patients, and may accelerate the decline of RKF, with detrimental consequences for their outcomes. This hypothesis has not been thoroughly investigated.

We present the results of a longitudinal study, oriented to disclose the potential effects of estimated PI during the first months of treatment on the rate of decline of RKF, in a relatively large sample of patients started on PD therapy.

Materials and methods

General design

Following a retrospective, observational design, we undertook a study oriented to disclose the potential influence of estimated mean PI during the first 4 months of treatment with chronic PD (main study variable) on the rate of decline of RKF (main outcome) of a relatively large sample of patients incident on PD in our centre during the period 2000–16. PI was estimated from the urea kinetic-based protein equivalent of urea nitrogen appearance (nPNA), while RKF was estimated from the mean of renal urea and creatinine clearances. We applied both univariate and multivariate strategies of analysis to control the confounding effect of other factors with a potential influence on the main study outcome.

This study fulfilled the ethic requirements of our centre for observational, retrospective studies. Oral informed consent was requested from patients, when feasible. The study complied with the principles of the Declaration of Helsinki for medical research.

Study population

We considered for analysis all adult (>18 years) patients starting PD therapy in our Unit during the period 2000–16, under five main inclusion criteria:

i. at least one estimation of PI (nPNA) under stable clinical conditions during the first 4 months on PD;
ii. RKF ≥2 mL/min at the inception of PD;
iii. a minimum follow-up of 6 months on PD;
iv. estimations of RKF available, at least, at the start of PD and 6 ± 1 months after initiation of therapy; and
v. oral informed consent for participation in the study (if patient still accessible).

The following exclusion criteria were applied:

i. denial of consent for participation in the study;
ii. patients incident on PD after receiving haemodialysis therapy for >2 months;
iii. patients incident on PD after renal transplant failure; and
iv. patients in whom control variables considered essential for the analysis [age, gender, presence of diabetes, Charlson's comorbidity score, basic anthropometrics (weight, height), proteinuria, treatment with antagonists of the renin–angiotensin–aldosterone axis (angiotensin-converting enzyme inhibitors-angiotensin-II receptor antagonists, ACEI-ARA)] could not be retrieved.

Study variables

The main study variable was the mean of nPNA values recorded during the first 4 months on PD. By definition, all patients had at least one estimation, 283 (84.2%) had two and 182 (54.2%) had three estimations, during this period. Values obtained <1 month after the resolution of a significant clinical event (including peritoneal infection) were not considered for analysis. nPNA values were obtained using a standard software (PD Adequest, Baxter Healthcare, Deerfield, IL, USA) [16]. This software normalizes PI according to current body weight. For this reason, we renormalized PNA values to the ideal body weight of the patients. For this purpose, we first calculated the baseline dry weight of the patients as current body weight minus absolute overhydration, when this parameter was available ($n = 202$) (multifrequency bioimpedance device, BCM, Fresenius, Bad Homburg, Germany); in the remaining cases, we applied an estimated value of +1.35 L (mean of available estimations). Then, ideal body weight was calculated according to the Hamwi method [17].

The main outcome variable was the rate of decline of RKF (mean of urea and creatinine clearances, normalized to body surface area). This variable was managed in two different ways.

i. Absolute variation of RKF: baseline minus last estimation available (with a limit at 24 months), divided by the number of months of follow-up between the applied values (rate of decline of RKF, in mL/min/month). For this purpose, we recorded follow-up estimations of RKF at baseline (n = 336, 100%), 6 (n = 336, 100%), 12 (n = 275, 81.8%) and 24 months (n = 175, 52.1%). For multivariate analysis, this variable was categorized according to its median value.
ii. Proportion of patients presenting a decline >50% of RKF after 12 months of follow-up (versus baseline). Expectedly, only patients with a minimal follow-up of 1 year (n = 275) were included for this part of the analysis. We renounced to our initial intention to apply development of anuria as an alternative outcome, because only 27 patients (8.0%) presented such complication during follow-up, preventing a consistent statistical management.

For both nPNA and RKF, the term ‘baseline’ refers to the first adequacy assessment, routinely performed in our Unit 2–4 weeks after initiation of PD.

We collected the following control variables at baseline: age, gender, presence of diabetes, standard Charlson’s comorbidity score, body mass index (dry body weight/height^2), blood haemoglobin, plasma albumin, plasma C-reactive protein, proteinuria, modality of PD (at 6 months), use of icodextrin for long dwell (baseline), use of biocompatible [low-glucose degradation products (GDP)] solutions, D/P 240′ creatinine [first peritoneal equilibration test (PET)], and treatment with ACEI-ARA drugs (any time during the first 6 months). Blood pressure (BP) levels were calculated from the mean values recorded during the first 2 months on PD therapy (in our unit, patients are instructed to record this parameter daily). Finally, we recorded episodes of peritoneal infection occurring during the period of follow-up of RKF.

Urea and creatinine levels in blood, urine and spent dialysate were calculated with the help of a standard autoanalyzer. The same applied for haemoglobin and albumin levels. C-reactive protein levels were estimated by immunoturbidimetry. Proteinuria was estimated using a standard pyrogalol red procedure.

Statistical analyses

Basic comparisons were produced according to standard parametric (Student’s *t*-test, analysis of variance) and nonparametric tests (Mann–Whitney, Kruskall–Wallis, χ^2 distribution, Fisher’s exact test, Spearman’s correlation coefficient), as needed. Univariate analyses focused on exploring the main correlates of mean nPNA during the first 4 months on PD, baseline RKF and its rate of decline. We then applied multivariate strategies of analysis to disclose any adjusted correlations between mean nPNA during the first 4 months on PD, on one side, and (i) the rate of decline of RKF during a follow-up period of 6 (minimum) to a limit of 24 months or (ii) the probability of a decline >50% of RKF after 1 year of follow-up, on the other. We did not consider the decline of RKF beyond 24 months due to the growing risk of selective biases brought by accumulating PD drop-out events. We used stepwise logistic regression to produce these analyses (dependent variables: rate of decline of RKF faster than median, and decline of RKF >50%, 1 year versus baseline). nPNA was managed as a continuous variable for the main multivariate analyses, but was secondarily categorized for a better clinical interpretation, into three levels, namely <1.00 [low PI (LPI)] ($n = 70$), 1.00–1.40 [average PI (API)] ($n = 162$) and >1.40 g/kg/day [higher PI (HPI)] ($n = 104$). We censored patients for further data collection in the following cases: death, PD stopped for >1 month for any reason, loss to follow-up and 2-year follow-up completed. The SPSS 19.0 software was used for data analyses.

Results

We included 336 patients for data analysis. The main characteristics of the study population are presented in Table 1. Diabetic nephropathy was the most frequent cause of CKD ($n = 94$, 28.0%), followed by chronic glomerulonephritis ($n = 69$, 20.6%), renal vascular disease ($n = 51$, 15.2%), cystic disorders ($n = 26$, 7.7%), tubulointerstitial disease ($n = 21$, 6.4%) and systemic conditions (including paraproteinemias) ($n = 13$, 3.8%). The aetiology of CKD was unknown in 62 cases (18.3%). Estimations of nPNA during the first 4 months correlated significantly ($r = 0.65$ baseline versus second estimation, $P < 0.0005$, Spearman), with a slight, yet significant trend to a decrease, during this period (1.24 baseline versus 1.21 g/kg/day second estimation, $P = 0.023$, paired *t*-test).

Table 1. Study population: baseline characteristics

N	336
Age (years)	59.3 (14.9)
Female gender (%)	116 (34.5)
Diabetes (%)	127 (37.8)
Charlson's comorbidity score	3.7 (1.8)
Automated PD at 6 months (%)	70 (21.0)
Icodextrin (%)	162 (48.2)
Low GDP solutions (%)	144 (42.9)
Overhydration (L) (n = 202)	1.35 (1.67)
Mean BP (mmHg)	96.7 (10.9)
ACEI-ARA drugs (%)	113 (33.6)
RKF (mL/min/1.73 m^2)	7.9 (3.2)
Proteinuria (g/day)	1.65 (1.77)
D/P 240′ creatinine (PET)	0.68 (0.14)
Plasma albumin (g/L)	36.7 (5.6)
Serum C-reactive protein (mg/dL)	0.46 (0.01–17.8)
Blood haemoglobin (g/dL)	10.9 (1.5)
Body weight (kg)	70.9 (11.9)
Height (m)	1.64 (0.09)
Body mass index (kg/m^2)	26.4 (4.5)
Ideal body weight (kg)	62.5 (10.0)
Mean nPNA, first 4 months (g/kg/day)	1.23 (0.33)
Number of patients with peritoneal infection during follow-up (%)	127 (37.8)

Figures denote mean values (SD) for numerical variables (except C-reactive protein, presented as median with range) and *n* (%) for categorized variables. Data at baseline except modality of PD (at 6 months) and nPNA (mean of first 4 months).

Univariate analyses

nPNA

Table 2 displays the univariate correlations among mean nPNA and the main control and outcome variables scrutinized. Male, older, overweight and comorbid patients presented significantly higher estimated PI rates. More interestingly, mean nPNA showed a direct correlation with baseline RKF (Figure 1) and moderate, yet significantly faster rates of decline of RKF (Figure 2).

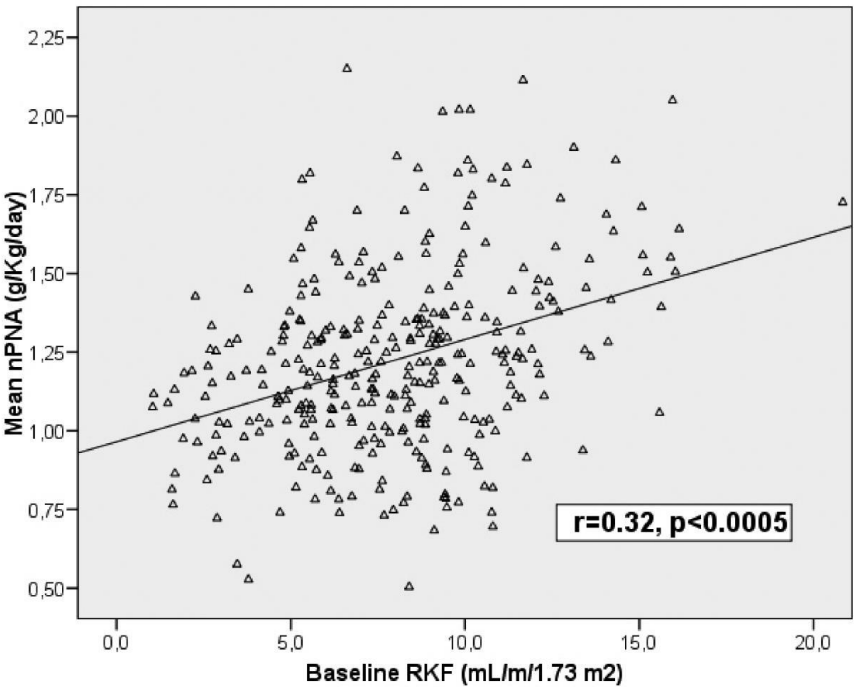

Figure 1. Univariate correlation between baseline RKF and mean nPNA during the first 4 months on PD (Spearman's correlation coefficient).

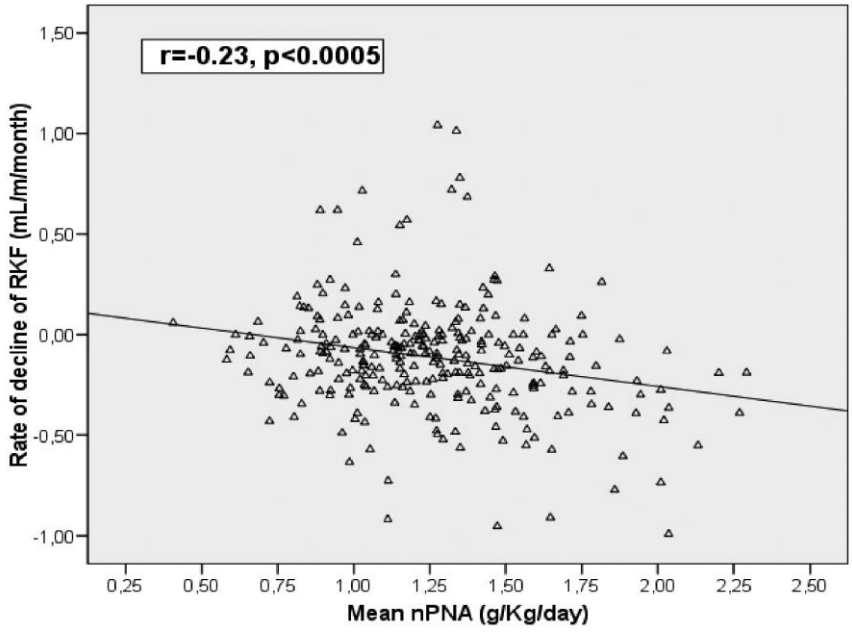

Figure 2. Univariate correlation between mean nPNA during the first months on PD and the rate of decline of RKF (Spearman's correlation coefficient).

Table 2. Univariate correlates of mean nPNA, RKF and its rate of decline

	Mean nPNA, first 4 months	**Baseline RKF**	**Rate of decline of RKF**
Age (years)	0.10 (0.09)	−0.01 (0.83)	0.03 (0.56)
Female gender (ref. male)	−0.14 (0.015)	−0.08 (0.17)	0.01 (0.83)
Diabetes (ref. no)	0.28 (0.0005)	0.05 (0.28)	−0.10 (0.056)
Charlson's comorbidity score	0.15 (0.01)	0.006 (0.91)	−0.05 (0.34)
Modality of PD (ref. CAPD)	−0.06 (0.35)	−0.01 (0.85)	−0.04 (0.47)
Icodextrin, baseline (ref. no)	0.06 (0.32)	−0.11 (0.035)	0.007 (0.89)
Low GDP solutions (ref. no)	0.07 (0.24)	0.16 (0.011)	−0.14 (0.022)
Overhydration, baseline (L) (n = 202)	0.06 (0.49)	−0.06 (0.32)	−0.11 (0.061)
Mean BP, baseline (mmHg)	−0.08 (0.30)	−0.02 (0.77)	−0.13 (0.021)
ACEI-ARA, baseline (%) (ref. no)	0.08 (0.20)	0.01 (0.80)	0.04 (0.46)
Baseline RKF (mL/m)	0.32 (0.0005)	–	−0.36 (0.0005)
Rate of decline of RKF (mL/min/month)	−0.23 (0.0005)	−0.36 (0.0005)	–
Proteinuria, baseline (g/day)	0.22 (0.0005)	0.01 (0.83)	−0.19 (0.0005)
D/P 240′ creatinine (baseline PET)	0.07 (0.25)	0.02 (0.71)	−0.05 (0.45)
Plasma albumin (g/L)	0.05 (0.39)	0.30 (0.0005)	−0.05 (0.35)
C-reactive protein (mg/dL)	−0.08 (0.19)	−0.13 (0.007)	0.03 (0.55)
Haemoglobin (g/dL)	−0.03 (0.61)	0.03 (0.63)	0.025 (0.61)
Body mass index (kg/m^2)	0.25 (0.0005)	0.05 (0.38)	−0.11 (0.03)
Peritoneal infection (ref. no)	0.03 (0.64)	−0.10 (0.08)	−0.04 (0.44)

Figures denote Spearman's correlation coefficients (P-value). For the rate of decline of RKF, negative coefficients denote faster decline. CAPD, continuous ambulatory peritoneal dialysis.

RKF

The mean rate of decline of RKF for the whole group was -0.13 ± 0.29 mL/min/month. Remarkably, 124 patients (37.1%) had a similar or improved RKF at the end of follow-up, when compared with baseline. The univariate correlates of baseline RKF and its ensuing rates of decline are presented in Table 2. Baseline RKF, proteinuria, mean BP levels, body mass index and mean nPNA were all direct univariate correlates of a faster decline of RKF, while diabetes and overhydration showed similar, non-significant trends.

A total of 61 patients were not available for analysis of the fractional decline of RKF at 1 year, due to kidney transplant ($n = 29$), death ($n = 10$), PD drop out ($n = 4$) or unavailability of an estimation of RKF at 12 ± 1 months ($n = 18$). Table 3 compares the main study variables in the remaining patients, according to the fractional decline of RKF during the first year on PD.

Multivariate analyses

Rate of decline of RKF

The results of multivariate, logistic regression analysis disclosed that, after controlling for the main determinants of decline of RKF, higher mean nPNA levels tended to be associated with a faster decline of RKF, close to statistical significance ($P = 0.058$) (Table 4). Baseline RKF was, by far, the most consistent predictor of its ensuing rate of decline, with a marked potential confounding effect on the association between nPNA and the outcome variable, due to its significant correlation with both variables (Table 2).

When nPNA was categorized, patients with HPI showed non-significant trends to a faster decline of RKF than those with LPI [odds ratio (OR) 1.61, 95% confidence interval (95% CI) 0.77–3.44, P = 0.20] and API (OR 1.72, 95% CI 0.96–3.18, P = 0.064), without apparent differences between LPI and API patients (OR 0.94, 95% CI 0.47–1.86, P = 0.85)

Table 3. Univariate comparisons according to fractional decline of RKF during the first year on PD

	Decline >50%	**Decline ≤50%**	**P-value**
N	69	206	
Age (years)	59.0 (17.8)	60.4 (13.2)	0.54
Female gender (%)	24 (34.8)	69 (33.5)	0.85
Diabetes (%)	25 (36.2)	81 (39.3)	0.81
Charlson's comorbidity score	3.6 (1.8)	3.7 (1.8)	0.68
Modality of PD (% automated)	17 (24.6)	37 (18.0)	0.24
Icodextrin (%)	33 (47.8)	102 (49.8)	0.82
Low GDP solutions (%)	49.4	36.5	0.023
Overhydration (L) (*n* = 185)	1.50 (1.71)	1.26 (1.50)	0.28
Mean BP (mmHg)	97.0 (10.7)	97.0 (10.2)	0.97
ACEI-ARA drugs (%)	20 (29.0)	76 (36.9)	0.19
Baseline RKF (mL/min/1.73 m^2)	7.8 (3.4)	8.4 (3.3)	0.25
Rate of decline of RKF (mL/min/month)	−0.36 (0.28)	−0.09 (0.19)	0.0005
Proteinuria (g/day)	1.96 (2.03)	1.45 (1.40)	0.023
D/P 240′ creatinine (PET)	0.68 (0.15)	0.68 (0.13)	0.95
Plasma albumin (g/L)	35.7 (6.2)	37.2 (4.8)	0.087
Serum C-reactive protein (mg/dL)	0.49 (0.10–14.20)	0.46 (0.03–17.80)	0.75
Blood haemoglobin (g/dL)	10.6 (1.5)	11.0 (1.3)	0.048
Body mass index (kg/m^2)	26.6 (4.0)	27.1 (4.6)	0.40
Mean of nPNA, first 4 months (g/kg/day)	1.31 (0.33)	1.21 (0.29)	0.032
Peritoneal infection (ref. no)	38.8	36.8	0.77

Figures denote mean values with standard deviation for numerical variables (except C-reactive protein, presented as median with range), and *n* (%) for categorized variables.

Table 4. Predictors of the rate of decline of RKF: multivariate, logistic regression analysis

	B	**OR**	**95% CI**	**P-value**
Baseline RKF (per mL/min/1.73 m^2)	0.26	1.29	1.17–1.43	0.0005
Proteinuria (per g/day)	0.20	1.22	1.02–1.45	0.022
Age (per year)	−0.02	0.98	0.96–1.00	0.055
Mean BP (per mmHg)	0.02	1.02	1.00–1.04	0.048
Mean nPNA (per 0.10 g/kg/day)	0.09	1.09	0.99–1.19	0.058
Constant	−4.99	0.007		0.0005

Best model: −2log likelihood 335.4, χ^2 56.35, P < 0.001. Outcome variable: rate of decline of RKF faster than median. First-order interaction terms not significant.

Fractional decay of RKF at the end of the first year on PD

Mean nPNA and proteinuria were identified as the only independent predictors of a decay >50% of RKF at the end of the first year on PD (Table 5). In this case, baseline RKF did not reach statistical significance for such outcome, but was included in the final model due to its potential confounding effect. As expected, in this case the trend was to a lower risk of the outcome in patients started on PD with higher levels of RKF.

After categorization of nPNA, patients with HPI showed clear trends to a faster decline of RKF than those with LPI (OR 2.14, 95% CI 0.93–5.38, P = 0.091) or API (OR 2.32, 95% CI 1.12–4.76, P = 0.023), again without apparent differences between LPI and API patients (OR 0.92, 95% CI 0.39–2.20, P = 0.86).

Table 5. Predictors of decline >50% of RKF at 1 year: multivariate, logistic regression analysis

	B	**OR**	**95% CI**	**P-value**
Baseline RKF (per mL/min/1.73 m^2)	−0.09	0.92	0.82–1.02	0.11
Proteinuria (per g/day)	0.16	1.18	1.02–1.42	0.028
Mean nPNA (per 0.10 g/kg/day)	0.14	1.15	1.04–1.27	0.006
Constant	−2.59	0.075		0.001

Best model: −2log likelihood 284.3, χ^2 13.62, P = 0.004. Outcome variable: rate of decline of RKF faster than median. Interaction term Proteinuria * Mean nPNA not significant.

Discussion

Restriction of PI has been a mainstay in the management of patients with CKD for several decades. The essential objectives of this measure are reducing the effects of uraemic toxicity, retarding the appearance and progression of some complications of the disorder, and, most remarkably, delaying the natural trend to a progressive decline of the glomerular filtration rate that characterizes most cases of CKD [5]. Many studies, some of them large randomized clinical trials, have provided variable degrees of support to the expected benefits of dietary protein restriction. Current perception indicates that former approaches based on very low protein diets may be counterproductive, particularly if not accompanied by ketoacid supplementation, as evidenced by a detrimental impact on patient survival [18]. Thus, moderate protein restriction represents now the most common approach, and is endorsed by current practice guidelines [1, 10]. However, the benefits of moderate protein restriction are still controversial [5, 19], because of contradictory reports (including several systematic reviews and metaanalyses) on the effects of this measure on progression of CKD and patient mortality [6–9]. Potential reasons for the discrepancies observed include differences among the populations involved in the studies, variable degrees of protein restriction, a relatively high incidence of non-compliance among patients participating in trials [5, 20] and, for more recent studies, a downplayed effect of protein restriction brought about by a reinforced implementation of complementary measures, including systematic prescription of ACEI-ARA drugs and improved control of acidosis and hyperphosphataemia [5, 18].

Current dietary recommendations for patients with CKD undergoing chronic dialysis emphasize the prevention and treatment of malnutrition and wasting [10, 11, 21]. On the contrary, preservation of RKF is not generally taken into consideration at the time of planning PI, despite the evidence linking this parameter to the outcome of haemodialysis [14] and, even more markedly, PD patients [15]. RKF at the initiation of PD, and even more its rate of decline, are

consistent independent predictors of mortality and PD technique failure [22]. On the other hand, the results of some studies suggest that a moderate, sensible limitation of PI may facilitate management of dialysis patients, and does not appear to bear negative effects on their nutritional status or outcomes, if nutritionally compromised individuals are excluded [23, 24]. On the contrary, stringent restriction of PI may entail a significant risk of mortality in these patients [24].

There is a marked paucity of data on the influence of PI on the time course of RKF in patients undergoing PD. In an exploratory survey aiming to disclose clinical predictors of the rate of decline of RKF in 146 PD patients, Johnson *et al.* [25] did not identify PI (as estimated from dietary questionnaires) as one such predictor although, in a secondary analysis, the authors observed that patients with higher levels of this variable presented an increased incidence of anuria during follow-up. On the other hand, in a small clinical trial, Jiang *et al.* [26] randomized 60 prevalent PD patients to one of: normal protein diet (1.0–1.2 g/kg/day), low protein diet (0.6–0.8 g/kg/day) and low protein diet supplemented with keto acids. Patients were followed for up to 1 year. Patients on a low protein-keto acid diet experienced a modest, yet significant slower decline of RKF, while there was no apparent difference between patients on a low versus normal protein diet. However, the practical estimated PI was very similar in the normal and low protein diet groups during follow-up, and the study may have been underpowered to uncover differences.

Our study provides evidence that higher levels of nPNA during the first months on PD associate a faster decline of RKF, suggesting that values above 1.4 g/kg/day may be particularly detrimental for this outcome. This effect was more apparent when the decline of RKF was explored as a fraction of baseline values than when absolute rates of decline were used as the outcome variable. The explanation for this relative discrepancy is not totally clear, but residual confounding by baseline RKF may have contributed significantly. RKF at the inception of PD showed a marked correlation with the absolute rate of decline of RKF (Table 1), which agrees with previous reports [25, 27], but had a less apparent association with its proportional decline over time (Table 3). On the other hand, baseline RKF kept a significant correlation with baseline and mean nPNA during the first months on PD (Table 2, Figure 1), again confirming the results of previous studies [24, 28, 29]. It has been argued that this latter association may be partly a consequence of mathematical coupling, but RKF has shown a similar correlation with PI in CKD patients, when the latter is estimated from dietary questionnaires [14, 28–30].

Interestingly, categorization of nPNA showed more consistent differences in the rate of decline of RKF between HPI and API groups than between the HPI and LPI groups. This finding should not be in contradiction to our main contention that excess PI may be detrimental for the rate of decline of RKF. Spontaneously low PI rates may mark specific subsets of patients who, for different reasons, may also tend to have an accelerated decline of RKF, downplaying any putative beneficial effect of restricted PI. On the other hand, the unequal size of the LPI, API and HPI groups may also have influenced statistical comparisons. We preferred to classify PI rates with a clinical meaning, rather than using a more conventional categorization by tertiles.

The present analysis posed some relevant methodological challenges. We acknowledge that, for some of them, we undertook debatable decisions. We did not apply time-dependent analysis to explore longitudinally the effect of nPNA, in the belief that the natural decline of RKF could itself bring about a progressive decay of PI. We censored follow-up for RKF at 2 years to minimize selective biases secondary to the rapidly growing incidence of PD drop out after this limit. It is conceivable that faster rates of decline of RKF could contribute to mortality and transfer to haemodialysis, in some of these cases. Another important issue is the convenience of normalizing nPNA to ideal body weight, which we applied to all our patients. Some guidelines consider compelling this correction only when the current dry weight is markedly lower (<90%) or higher (>115%) than ideal weight [1, 21]. This caution, neglected in some former studies, is very relevant, because normalization of PI to current body weight in undernourished, overweight or overhydrated individuals results in unrealistic estimations [12]. The advantages and drawbacks of different methods of standardization of PI have been reviewed in detail elsewhere [31].

In addition to the questions commented on in the previous paragraph, our study suffers some other significant limitations. These include a single-centre, retrospective design. Dietary surveys offer some advantages at the time of estimating PI, avoiding risks of mathematical coupling with some variables, but this method has also a limited accuracy, and urea kinetics is generally recognized as a reliable method to evaluate PI in stable CKD patients [4, 32] and, particularly, in PD patients [33, 34]. We cannot exclude that, in some of our patients, undetected catabolic states may have flawed part of the estimations of PI. The use of a mean of two to three nPNA values as the main study variable in the majority of cases should be expected to mitigate this potential bias. Isolated estimations of nPNA are unsuitable for evaluation of PI and guidance of dietary recommendations in individuals sustaining a suspected catabolic phase and, in general, in severely malnourished and comorbid patients. On the other hand, among the strengths of this study, we should mention a powered sample and a high quality and completeness of the main control variables, permitting consistent and reliable conclusions for the analyses performed.

In conclusion, our study provides evidence that high rates of PI may associate a faster decline of RKF in patients starting PD. Our results suggest the convenience of keeping a balance between sufficient protein ingestion, to prevent malnutrition and wasting, and sensible restriction for stable, adequately nourished patients with rates of intake in the higher range or above-recommended allowances. Dietary education and close monitoring of PI by means of urea kinetics, dietary surveys or any other validated method represent adequate instruments, for these purposes. Further studies will be necessary to validate our results

Conflict of interest statement

None declared

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