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Original Article

ORIGINAL ARTICLE

Clinical management of patients on peritoneal dialysis in Italy: results from the ATENA study

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Abstract

Background: In Italy, few studies have examined the clinical management of peritoneal dialysis (PD) patients, resulting in a lack of information and awareness.

Methods: A total of 378 PD patients (64.7 ± 14.3 years, 58.9% males) were enrolled across 15 centres in a 12-month retrospective and 6-month prospective study. The primary objective was to evaluate the achievement of Kidney Disease Outcomes Quality Initiative and Kidney Disease Improving Global Outcomes guidelines on recommended target values for anaemia, high blood pressure and mineral metabolism. Comorbidities, hospitalizations, treatment and quality of life were also assessed.

Results: Frequent comorbidities included hypertension (87.8%) and cardiovascular disease (39.7%). Peritonitis was the leading cause of hospitalization [12 admissions per 100 person-years (95% confidence interval 9.3–15.2)]. At 6 months, anaemia corrected by erythropoiesis-stimulating agents was observed in 30% of patients and 73% received erythropoiesis-stimulating agents. Systolic and diastolic blood pressures were recorded in 50% and 20% of patients, respectively. Sixty-four percent of echocardiograms revealed left ventricular hypertrophy and 30% of patients had vitamin D <10 ng/mL. Medication to treat intact parathyroid hormone (PTH) included calcitriol (36.3%), paricalcitol (29.2%), cholecalciferol (23.6%) and cinacalcet (21.5%). In a subgroup of patients matched for baseline PTH treated for 1 year, a significant reduction in PTH with paricalcitol (−41%; $P < 0.001$) but not cinacalcet (+2%; $P = 0.63$) was observed. Comparison of quality of life domains revealed significant differences for symptoms ($P = 0.049$), cognitive function ($P = 0.019$) and social support ($P = 0.04$) (baseline versus 6 months).

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Conclusions: Hypertension and cardiovascular diseases were frequent comorbidities and peritonitis was the leading cause of hospitalization. Secondary hyperparathyroidism and anaemia were common, thus necessitating frequent monitoring of PTH, calcium, phosphorus and haemoglobin.

Key words: anaemia, chronic kidney disease, metabolic bone disorders, peritoneal dialysis, secondary hyperparathyroidism

Introduction

The incidence of end-stage renal disease (ESRD) is increasing in industrialized countries [1]. Risk factors for ESRD are an ageing population, diabetes and hypertension [2]. The incidence of renal replacement therapy (RRT) in Europe according to 2012 ERA-EDTA estimates is 133 per million persons (pmp) [3]. According to data from the Italian Dialysis and Transplantation Registry (RIDT) for 2009 regarding incident patients, 8461 patients were on RRT; 88% on haemodialysis (HD) and 12% on peritoneal dialysis (PD) [4].

The Italian Study Group of Peritoneal Dialysis reported an incidence of PD of ∼20% and a prevalence of 15% [5, 6]. This discrepancy in the use of RRT methods is caused by several factors and, in Italy, PD continues to be used heterogeneously [4]. Due to recent evidence demonstrating advantages offered by PD, it is important to assess the relative advantages and disadvantages of RRT methods [7, 8].

Few epidemiological studies have assessed the clinical management of patients on PD in Italy [6, 9, 10]. These were single-centre studies [10] or lacked data on therapeutic management, comorbid diseases or outcome measures [6, 9] or were performed 10–20 years ago [9]. Mortality from cardiovascular disease (CVD) is higher in patients with chronic kidney disease (CKD) compared with the general population [11], but, unlike patients on HD, ESRD patients receiving PD present lower mortality rates during the first 2 years of treatment; rates then rise over subsequent years [8, 12–14]. Risk factors for CV mortality in these patients include additional factors linked to the presence of ESRD and others that are secondary to RRT and specific to PD [15]. High-glucose exposure caused by PD treatment may also lead to the development of diabetes and left ventricular hypertrophy (LVH) [16]. Patients on PD generally experience weight gain, dyslipidaemia, hypertension and anaemia, the latter caused by endogenous erythropoietin deficiency secondary to ESRD and by low-serum iron levels [17, 18].

Peritonitis, a severe complication in PD patients, often results in hospitalization, loss of peritoneal catheter function and impairment of the peritoneal membrane [19].

Secondary hyperparathyroidism (SHPT) is another frequently observed complication in ESRD patients, characterized by mineral bone disorders associated with the presence of vascular calcifications and consequent CVD [19–22]. Vitamin D metabolism is altered [23] and patients on PD often present significant deficiency of vitamin D because of diet restrictions, lack of exposure to sunlight and loss of effluents through dialysis [24]. Vitamin D deficiency is recognized as another CV risk factor [25].

The aim of this epidemiological study was to observe the clinical and therapeutic management of PD patients in Italy, thereby providing a comprehensive picture related to clinical practice that may lead to the revision of current guidelines and improved therapeutic management of these patients.

Materials and methods

Patients

ATENA was a longitudinal, non-interventional, epidemiological investigation performed between February 2013 and March 2014. Adult outpatients presenting with ESRD and on treatment with PD for at least 12 months were selected by nephrologists across 15 Italian clinical sites. Patients were followed as per current clinical practice and no additional diagnostic or monitoring procedures were applied unless permitted by Italian guidelines for non-interventional studies [26]. The choice of medical treatment, if any, was made independently by the physician during routine practice.

Inclusion criteria included patients on PD treated for at least 12 months, >18 years of age and who signed an informed consent form.

Exclusion criteria included patients enrolled in clinical trials or who already participated in the survey, patients who switched from HD to PD, organ transplantation patients and patients presenting with diseases that reduce life expectancy to <1 year. Ethics committee approval from all participating centres and written informed consent were obtained from every patient, in compliance with Legislative Decree 196/2003. This study complies with the ethical standards in the Declaration of Helsinki.

Study design

The total scheduled observational period was 18 months. Data were collected and recorded into an electronic case report form for a total of four data reporting time points: two retrospective data collections at −12 months and −6 months, one cross-sectional data collection at baseline and one prospective data collection at +6 months after baseline. During outpatient clinic visits, data were collected on demographics and lifestyle parameters, anthropometric variables, data relating to dialysis treatment, dialysis method and renal status, in addition to CKD and mineral bone disorder (CKD-MBD) and lipid parameters.

Furthermore, information on medical history (duration of dialysis treatment and concomitant diseases) and incident clinical data (ongoing pharmacological treatments, laboratory data and hospitalizations related to dialysis (from −12 months to +6 months), switch to HD or renal transplant and death (from baseline to +6 months) were collected. Each participating subject was also asked to complete the Kidney Disease Quality of Life Short Form questionnaire, version 1.3 (KDQOL-SF 1.3) at baseline and after 6 months.

Study objectives and parameters measured

The primary objective of this study was to describe changes in clinical parameters compared with reference values according to international guidelines for patients on PD for the following aspects: anaemia, hypertension and CKD-MBD [21, 23]. Normal PTH values were 2–9 times the upper reference limit for the assay, according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines [23]. A secondary objective was to describe comorbidities, mortality and hospitalizations (i.e. infectious, CVD and MBDs). The QOL in PD patients was

assessed by administration of a QOL questionnaire at baseline and after 6 months (KDQOL-SF 1.3) [27].

Statistical analysis

Sample size was calculated taking into consideration an ~9% prevalence of PD in the dialysis patient population (~4000 patients) [4]. A sample size of 375 subjects was estimated to allow for a 95% confidence interval (CI) of ±4.9% for the most undefined response (50%). Data are presented as mean ± SD, median and interquartile range (IQR) or percentage. Within patient, comparisons of continuous variables were performed by the Friedman test. The incidence of hospitalizations (and 95% CI) due to different causes was expressed as the number of admissions per 100 patient-years. The total person-time was calculated from the individual follow-up time taking into account the date of censoring and death. Satisfaction of the subject relative to his/her QOL was rated based on questionnaire scores [27]. Comparisons between scores for different domains (baseline versus 6 months) were assessed by paired Wilcoxon rank test. Quoted P-values are two-tailed; *n* values refer to the number of patients. $P < 0.05$ was considered statistically significant. Analysis was performed using SAS version 9.2 for Windows (SAS Institute, Cary, NC, USA).

Results

Baseline demographic and clinical characteristics

A total of 378 patients were included in the ATENA study and 42 patients (11.1%) withdrew before study completion. One subject was not evaluable due to violation of inclusion/exclusion criteria. Reasons for patient withdrawal (total person-time 180 patient-years) were death [*n* = 16, i.e. 8.9 deaths/100 person-years (95% CI 5.1–14.4)], haemodialysis [*n* = 14 (in 9 cases because of peritonitis), i.e. 7.8 patients/100 person-years (95% CI 4.3–13.0)] and renal transplant [*n* = 10, i.e. 5.6 patients/100 person-years (95% CI 2.7–10.2)]. Two patients were lost to follow-up. Patient baseline demographic and clinical characteristics are presented in Table 1. The mean age of patients at baseline was 64.7 ± 14.3 and 58.9% (*n* = 223) were males. Of the patients, 97.1% were Caucasian and the mean duration of PD (before baseline visit) was 39.7 ± 29.1 months. The most frequent comorbid diseases were hypertension [87.8% (*n* = 332)], presence of CVD (including LVH) [39.7% (*n* = 150)], dyslipidaemia [24.1% (*n* = 91)], type 1 diabetes [4.2% (*n* = 16)], type 2 diabetes [20.1% (*n* = 76)] peritonitis [11.9% (*n* = 45)] and malignancies [11.1% (*n* = 42)]. At baseline, the most frequent concomitant medications included anti-anaemic agents [80.1% (*n* = 303)], antacid agents [75.4% (*n* = 285)], diuretics [74.6% (*n* = 282)] and lipid-lowering agents [59.8% (*n* = 226)]. Approximately half of the patients received beta-blockers or calcium (Ca) channel blockers [48.7% (*n* = 184)] for either treatment (Table 1), other antihypertensives [32.6% (*n* = 123)] or antidiabetic agent [19.8% (*n* = 75)].

Table 1. Baseline demographic and clinical characteristics

Characteristic	Value
Male gender, *n* (%)	223 (58.9)
Age (years), mean ± SD	64.7 ± 14.3
BMI (kg/m^2), mean ± SD	26.6 ± 4.8
Systolic blood pressure (mmHg), mean ± SD	135.4 ± 18.7
Diastolic blood pressure (mmHg), mean ± SD	78.1 ± 11.6
Ethnic origin, *n* (%)	
White	367 (97.1)
Black	4 (1.06)
Hispanic	4 (1.06)
Asian	3 (0.79)
Current cigarette smoker, *n* (%)	46 (12.2)
Alcohol consumption, *n* (%)	27 (7.2)
Dialysis duration (months), mean ± SD	39.7 ± 29.1
Comorbid diseases, *n* (%)	
Hypertension	332 (87.8)
Diabetes	92 (24.3)
Dyslipidemia	91 (24.1)
Peritonitis	45 (11.9)
Malignancies	42 (11.1)
CVD	150 (39.7)
Coronary artery disease	41 (10.8)
Left ventricular hypertrophy	12 (3.2)
Arrhythmia	11 (2.9)
Peripheral artery disease	5 (1.3)
Concomitant medication, *n* (%)	
Anti-anemic agent	303 (80.1)
Antacid agent	285 (75.4)
Loop diuretic	282 (74.6)
Lipid-lowering agent	226 (59.8)
Vitamins	215 (56.9)
Antithrombotic agent	189 (50)
Beta-blocker	184 (48.7)
Calcium channel blocker	184 (48.7)

Primary endpoints

Anaemia

Median haemoglobin (Hb) levels significantly decreased over the four visits (11.6 at −12 months, 11.4 at −6 months, 11.4 at baseline and 11.3 at +6 months; P = 0.006). In ~30% of patients, Hb levels were below the lower limit of the normal range (≤11 g/dL) across the four visits (Figure 1A). In contrast, most patients (~70%) maintained serum iron levels in the normal range over the four visits. In a few patients (2–6 patients), iron levels were above the upper limit over the four visits, whereas between 27 and 30% of patients (72–88 patients) showed values below the lower limit over the study period (Figure 1B). Iron levels did not change over the four visits.

Hypertension and LVH

Levels of systolic and diastolic blood pressure did not change over the four visits. Approximately 50% (46.5–52.2%) of patients had high systolic blood pressure (>140 mmHg), whereas ~20% (18.7–23.3%) of patients had high diastolic blood pressure (>90 mmHg) during all observations. LVH was observed in 64% echocardiograms performed and a left ventricular ejection fraction (LVEF) <45% was observed in ~10% of patients over the study period. LVEF did not change over the four visits.

Mineral metabolism diseases

Median levels of serum PTH, Ca and phosphate did not significantly change in patients over the four visits (Table 2 and Figure 2). Changes in the proportion of patients within cut-off ranges for PTH according to KDIGO and KDOQI guidelines are shown in Figure 2A and B, respectively. Approximately 67% of patients had PTH values within the normal range according to KDIGO guidelines (maximum 69% at the −6 months assessment) (Figure 2A). In contrast, only ~34% (32.4–38%) had normal

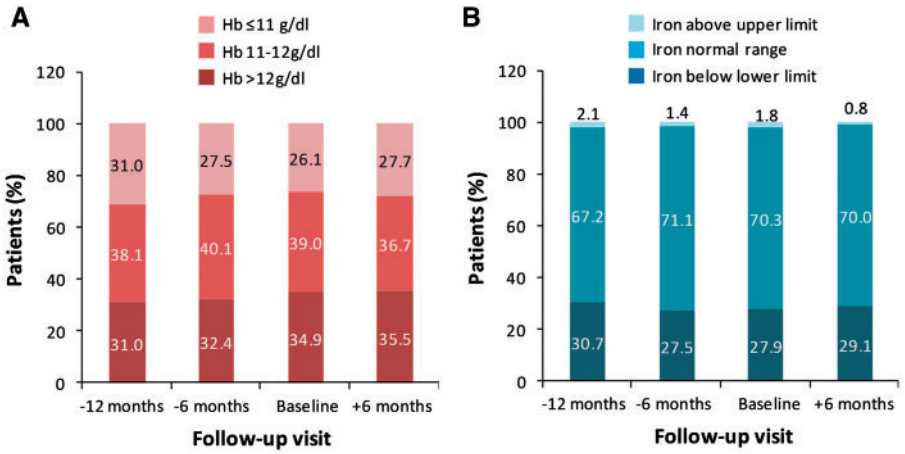

Fig. 1. Haemoglobin (A) and serum iron levels (B) over the four visits.

Table 2. Levels of biochemical parameters over the four visits

	−12 months			−6 months			Baseline			+6 months			
Parameter	*n*	Median	IQR	*n*	Median	IQR	*n*	Median	IQR	*n*	Median	IQR	P-value
PTH (pg/mL)	318	238	133–377	331	228	128–367	322	218	134–370	284	219	139–362	0.65
Phosphorus (mg/dL)	361	4.9	4.1–5.7	373	4.8	4.0–5.7	372	4.9	4.1–5.7	331	4.8	4.0–5.7	0.44
Ca (mg/dL)	310	9.1	8.5–9.6	311	9.1	8.6–9.6	310	8.9	8.4–9.5	277	9.0	8.6–9.6	0.095
25(OH) Vit D (ng/mL)	129	15.7	9.9–23.9	131	14.5	8.9–21.0	132	14.7	8.1–21.3	148	15.8	9.0–24.0	0.78
CRP (mg/dL)	264	0.40	0.20–1.28	290	0.43	0.20–1.54	269	0.44	0.22–1.29	248	0.50	0.30–1.91	0.13
HbA1c (mg/dL)	147	6.0	5.4–6.7	153	6.0	5.4–6.7	156	6.0	5.5–6.6	140	5.7	5.1–6.4	0.01
Albumin (mg/dL)	350	3.7	3.2–4.0	358	3.6	3.2–4.0	357	3.4	3.1–3.8	327	3.5	3.2–3.8	<0.001
Creatinine (mg/dL)	364	7.5	6.2–10.0	363	8.0	6.2–10.2	372	8.4	6.6–10.6	330	8.6	6.8–10.6	<0.001
Ultrafiltration daily volume (mL/day)	351	600	270–1000	353	600	300–1000	356	700	350–1000	325	750	400–1100	<0.001
Dialysis adequacy (Kt/V)	256	2.1	1.8–2.4	179	2.1	1.9–2.4	254	2.1	1.8–2.4	177	2.0	1.8–2.3	0.15
Dialysis adequacy (CrCl)	252	66.7	54.1–90.9	178	63.7	51.4–82.7	251	66.7	51.0–90.0	175	63.3	52.0–82.0	<0.001
Diuresis (mL)	361	1200	700–1725	363	1200	540–1600	371	1000	400–1500	328	1000	400–1500	<0.001

Ca, calcium; 25(OH) Vit D, circulating 25-hydroxyvitamin D; HbA1c, glycosylated haemoglobin A1c; CrCl, creatinine clearance.

PTH according to KDOQI guidelines suggested ranges (150–300 pg/mL) (Figure 2B).

Serum phosphate levels did not change over the four visits (Table 2). Few patients had phosphorus values below the lower limit (<3.4 mg/dL), whereas patients with values above the upper limit (>5.2 mg/dL) were between 33% (−6-month visit) and 38% (baseline) (Figure 2C). 17% (15.8–18.8%) reported Ca values below the lower limit (<8.4 mg/dL), whereas 5.4–8.4% were above the upper limit (>10.2 mg/dL) (Figure 2D). No statistically significant difference was observed in median levels of serum Ca over the four visits (Table 2).

Other biochemical and clinical parameters

Other biochemical and clinical parameters over the four visits are shown in Table 2. One-quarter of patients presented with deficient levels of vitamin D (<10 ng/mL) over the four visits, while ∼60% of patients had insufficient levels (10–30 ng/mL) and only 10% (8.4–10.9%) had normal levels (>30 ng/mL). Levels of vitamin D or C-reactive protein (CRP) did not change over the four visits (Table 2). CRP levels for the majority of patients (90%) were within the normal range (<5 mg/L). In contrast, albumin levels significantly changed over the four visits ($P < 0.001$) (Table 2). Furthermore, the proportion of patients with low albumin levels (<4 g/dL) increased from 75% at −12 months to 83% at the last visit, +6 months. The proportion of patients with HbA1c >7% was ∼20% and a significant reduction was observed across the study period ($P = 0.01$). Body mass index (BMI) increased slightly over the study period ($P = 0.02$), whereas levels of lipid parameters (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides) did not change.

Dialysis and renal parameters

Creatinine, ultrafiltration daily volume and number of exchanges increased in a time-dependent manner over the study period, whereas dialysis adequacy and diuresis decreased over the four visits (Table 2).

Secondary endpoints

Hospitalization

Over the study period (total person-time 558 patient-years), 250 hospitalizations were recorded totalling an incidence rate of 44.8 admissions per 100 person-years (95% CI 39.4–50.7). The mean hospital stay was 10 ± 8 days [median 8 days (IQR 4–13 days)].

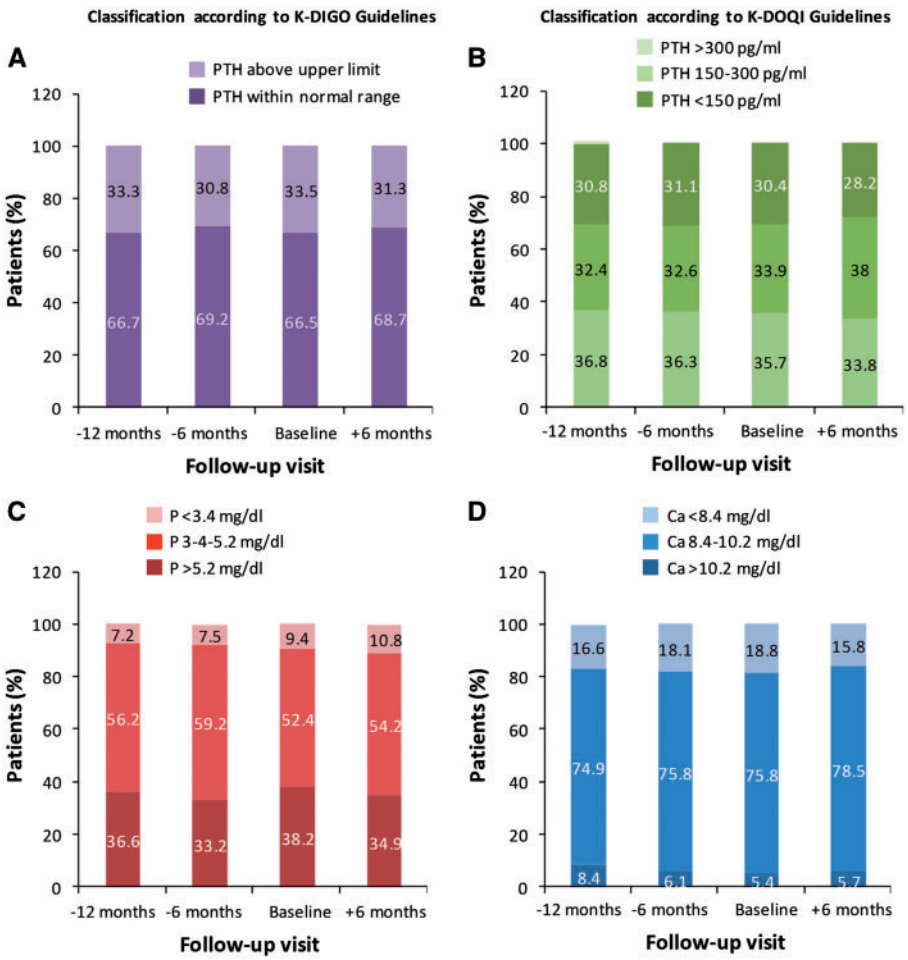

Fig. 2. PTH (A-B), P (C) and Ca (D) levels over the four visits.

Peritonitis was the leading cause for hospitalization [12 admissions per 100 person-years (95% CI 9.3–15.2)] followed by CV diseases [8.4 admissions per 100 person-years (95% CI 6.2–11.2)]. Other reasons included electrolyte balance alterations [2.9 admissions per 100 person-years (95% CI 1.6–4.7)], other infections excluding peritonitis [2.5 admissions per 100 person-years (95% CI 1.4–4.2)], malfunctioning PD catheter [2.3 admissions per 100 person-years (95% CI 1.2–4.0)] and reasons other than these [16.5 admissions per 100 person-years (95% CI 13.3–20.2)].

Management of anaemia and MBD

At 6 months, not or inadequately corrected anaemia by erythropoiesis-stimulating agents (ESAs; Hb $\leq$ 11 g/dL) was observed in 30% of patients and 73% received ESAs. The proportion of patients by Hb level cut-off ranges following treatment with erythropoietin and/or iron is shown for the four visits in Supplementary Figure 1. While the proportion of patients treated with ESAs (or ESAs + iron) increased over the four visits (~30% at −12 months to ~60% at +6 months), the proportion of patients receiving iron remained unchanged while patients who did not receive either ESAs or iron decreased over the four visits (Supplementary Figure 1).

Approximately 30% of the subjects had SHPT. Medications used to treat PTH included calcitriol (36.3%), paricalcitol (29.2%), cholecalciferol (23.6%) and cinacalcet (21.5%). The most frequent Ca phosphate-binding agents included Ca carbonate (16.2%) and Ca acetate/magnesium carbonate (10.1%), whereas the most common non-calcium-based phosphate binder used was sevelamer (46.4%).

Changes in levels of PTH, Ca and phosphorus for the four visits are shown for the different treatment modalities in Supplementary Figure 2. Vitamin D activators and the calcimimetic agent (cinacalcet) tended to reduce PTH levels in a time-dependent manner (Supplementary Figure 2A), whereas Ca and phosphorus levels remained unchanged with the different treatment options for the four visits (Supplementary Figure 2B and C). A subgroup of patients matched for baseline PTH levels who initiated therapy in the last 12 months with paricalcitol or cinacalcet was specifically identified for comparing the efficacy of these two drugs for reducing PTH values over a 1-year period. A significant reduction in PTH (from 435 to 257 pg/mL, −41%; $P < 0.001$) with paricalcitol (1.5 μg/day) but not with cinacalcet (37.2 mg/day) (from 462 to 473 pg/mL, +2%; $P = 0.63$) was observed, while Ca and phosphorus levels remained unchanged (Figure 3A and B).

QOL

QOL was evaluated by the KDQOL-SF 1.3 questionnaire [35, 36]. Paired comparisons using Wilcoxon rank analyses revealed significant differences for symptoms ($P = 0.049$), cognitive function ($P = 0.019$) and social support ($P = 0.04$) between the baseline and the +6-month assessment. No differences were observed in the remaining paired comparisons.

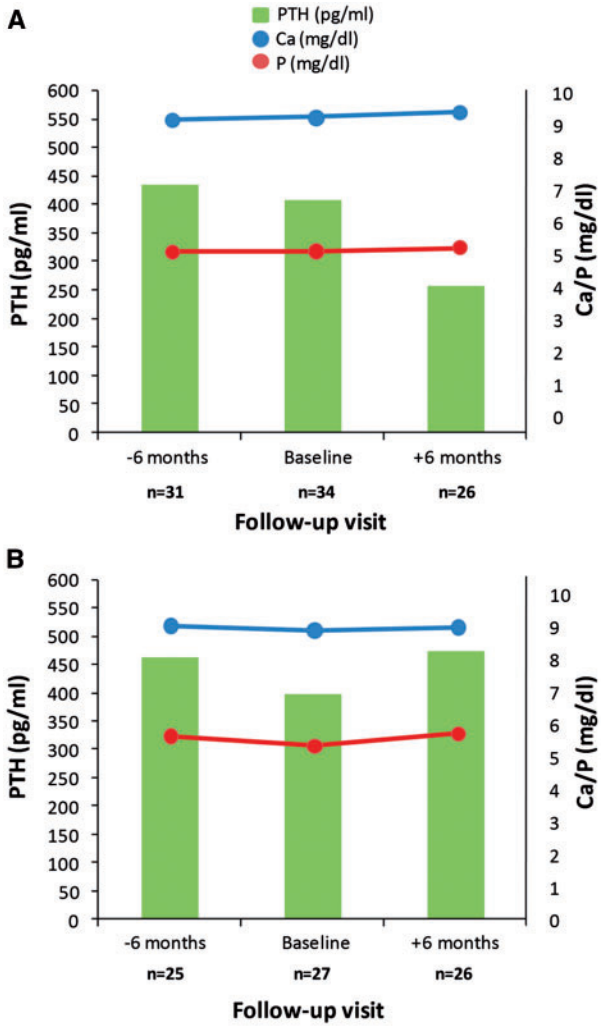

Fig. 3. Effect of (**A**) paricalcitol and (**B**) cinacalcet on PTH, Ca and phopshorus (P) in patients started with these therapies in the last year of the study.

Discussion

Several observational studies in Italy have examined the clinical management of HD patients, although few have examined the clinical outcome and management of PD patients [6, 9, 10].

Our study documents that a large percentage of PD patients (87.8%) have hypertension, despite the fact that a similar proportion receive antihypertensive medications. The prevalence of hypertensive patients is similar to that reported in the literature (88.1%) as well as the percentage of patients receiving medications (71%) [28]. In this study, patients show ∼1000 mL/day of diuresis after 2.6 years of treatment and 74.6% of them take loop diuretics. Furthermore, patients reach dialysis adequacy targets (Kt/V and creatinine clearance) and residual renal function contributes significantly to this result [29].

We observed that 73% of PD patients receive ESAs for the correction of anaemia, higher than that observed in the American population, where only 20% are treated with ESAs [30]. Moreover, our results confirm the low percentage of PD patients taking iron, compared with HD patients, due to less blood loss during extracorporeal procedures and minor diagnostic tests [31].

It is worth noting that ∼25% of patients presented with deficient levels of vitamin D (<10 ng/mL) over the four visits, while 60% of patients had insufficient levels (10–30 ng/mL): loss via peritoneal fluid as a contributing factor to low vitamin D levels in PD patients has previously been demonstrated [32].

PTH levels were significantly increased in 30% of patients. Vitamin D compounds improve biochemical parameters and are recognized to be effective in decreasing PTH levels [33]. In the ATENA study, ∼20% of patients were receiving cinacalcet alone or in combination with paricalcitol. The high baseline PTH levels of patients receiving the calcimimetic agent suggest that this drug was given to patients that did not respond to vitamin D therapy.

A further finding that emerged from our study was the stability of Ca and phosphorus levels, regardless of the type of therapy administered: >30% of patients had phosphorus levels >5.2 mg/dL. This result may be of particular interest because it indicates that despite significant residual renal function, phosphorus control in PD patients is difficult to maintain [34].

The presence of underlying inflammation, represented by CRP levels higher than the normal range, was observed in ∼10% of PD patients. These values are lower than those reported in the literature [35], suggesting a role for the more biocompatible dialysis solution (low GDP) introduced in recent years [36].

Peritonitis is recognized as one of the main reasons for hospitalizations [19]. In our study, the rate of peritonitis (one episode every 100 months) was lower compared with ISPD guidelines (one episode every 41–52 months) [37]. This favourable outcome may be explained by the experience (at least 25 PD patients) of the Italian PD centres selected for this study.

The presence of CV events was the second cause for hospitalizations. LVH, observed in ∼60% of patients who performed echocardiograms, predicts an increased risk of mortality and is associated with an increased risk of heart failure [38].

Results from the QOL questionnaire show that the worsening of symptoms and cognitive function increases the demand for social support. However, the short period between the two visits (6 months) may represent an important weakness.

Potential limitations of the ATENA study include the possible presence of confounding factors, such as drug dose, which are not controlled in an observational study, the absence of a centralized testing laboratory and selection of the 15 dialysis centres based on a specific set of criteria, including the ability to conduct the survey and the availability of an adequate number of patients in the centre. Although these potential limitations should be considered in future studies, they do not significantly affect the ability of the ATENA survey to identify trends in the management of SHPT in patients undergoing PD across the Italian peninsula.

This study is of particular value as it provides longitudinal data over a period of 18 months in patients with PD. Furthermore, this is the longest observational longitudinal study in Italy in a relatively large number of patients, strengthened also by the low number of dropouts.

In conclusion, hypertension and CVD are frequent comorbidities in these patients and peritonitis was the predominant cause of hospitalization. SHPT and anaemia were frequent and it is therefore important to regularly monitor Hb, PTH, Ca and phosphorus levels.

Supplementary data

Supplementary data are available online at http://ckj.oxfordjournals.org.

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Conflict of interest statement

AbbVie participated in the study design, interpretation of data and writing of the publication. U.L.P., A.M.C. and G.G. are employees of AbbVie and may own AbbVie stock options. A.P. was an employee of AbbVie. C.C., E.G.G., R.D. and F.C. have no conflict of interest. R.R. is a consultant for Baxter, Roche and AbbVie.

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