

Residual Renal Function Plays an Important Role in Regulating Parathyroid Hormone in Patients on Continuous Ambulatory Peritoneal Dialysis

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In the past, hyperparathyroidism was not generally a major problem in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). However, in conjunction with disturbances in serum phosphate, Ca, and Ca×P product, hyperparathyroidism has become a serious problem in the cardiovascular diseases of patients with end-stage renal disease—even patients undergoing CAPD. We retrospectively evaluated the first 5 years on CAPD for 17 patients who started and continued dialysis between April 1995 and September 2003. Of these 17 patients, 3 underwent parathyroidectomy. During their clinical course, all of the patients experienced a decline in residual renal function (RRF) that was significantly negatively correlated with their levels of serum Ca and intact parathyroid hormone. Based on these findings, we suggest that RRF is an important factor for the regulation of Ca–P metabolism in patients on CAPD.

Key words

Parathyroid hormone, residual renal function, calcium, phosphate, CAPD

Introduction

Recently, the importance of residual renal function (RRF) in continuous ambulatory peritoneal dialysis (CAPD) has been emphasized (1). The important association between RRF and survival in dialysis patients was first reported by Maiorca *et al.* (2). Wang *et al.* (3) clearly demonstrated that anuric CAPD patients had metabolic and cardiovascular profiles that were more adverse than those of patients with

preserved RRF. In their experience, the degree of RRF was strongly associated with phosphorus control in CAPD patients (4). The role of phosphate had previously been discussed in conjunction with bone metabolism, but that discussion has now been extended to include vascular calcification (5).

In CAPD patients, hyperphosphatemia has not usually been recognized, because peritoneal dialysis clearance contributes significantly to phosphorus control. In addition, CAPD has been shown to clear significant amounts of parathyroid hormone (PTH) from serum (6). But others have reported no change (6), an increase (7), or a variable response (8) in PTH levels.

In the present study, we retrospectively examined the association between PTH level and RRF in CAPD patients. We also evaluated the relationship between PTH and the status of the parathyroid glands.

Patients and methods

We retrospectively evaluated the first 5 years on CAPD for 17 patients who began and continued dialysis between April 1995 and September 2003. Before the start of CAPD therapy, ultrasonographic examination of the parathyroid glands was performed, and no patient exhibited enlarged glands.

During the study, all subjects were asked to continue their usual dietary habits. Mean daily dietary intake was determined from individual 24-hour food records during a 3-day period. Daily dietary protein intake was approximately 1 g/kg, and daily energy intake was more than 25 kcal/kg. Daily salt intake was restricted to between 7 g and 9 g.

To maintain adequate control of uremia, weekly creatinine clearance calculated by PD Adequest (Baxter Healthcare, Tokyo, Japan) was evaluated

every 3 months, and the dose of PD (fluid quantity and frequency of bag exchanges) was adjusted to reach a weekly creatinine clearance of approximately 60 L. If the weekly creatinine clearance fell below 45 L despite a full dose of PD, once-weekly hemodialysis was introduced (9).

Patients were instructed to visit the outpatient CAPD clinic every 2 weeks, and at those visits, the patients' records of body weight, urine volume, and dialysate drain volume were checked.

Evaluation of biochemical data

At the beginning of each month, serum creatinine, blood urea nitrogen, total protein, serum albumin, serum electrolytes, and alkaline phosphatase were measured. During each 6-month period, laboratory values were recorded. Six-month means were calculated for those variables. Parathyroid hormone (PTH) levels (intact molecule assay), serum cholesterol, and triglycerides were measured every 6 months.

Correction of anemia

Recombinant human erythropoietin was administered subcutaneously weekly or during alternate weeks, and the doses were adjusted monthly. Patients were given oral iron supplementation if they were diagnosed as iron-deficient. Hemoglobin levels were maintained at about 10.0 g/dL.

Ca metabolism

Patients who had PTH levels higher than 200 pg/mL were treated with 1,25-dihydroxyvitamin D₃; patients with levels of Ca×P product lower than 70 pg/mL were treated with CaCO₃ to reduce hyperphosphatemia.

Lipid metabolism

Lipid-lowering drugs (mainly statin derivatives) were administered if serum cholesterol levels rose above 240 mg/dL.

Blood pressure control

Antihypertensive agents, including angiotensin receptor blockers (10,11), were used to control blood pressure to below 140/90 mmHg.

Statistics

Data are expressed as mean ± standard error of the mean. Analysis of variance, Student *t*-test with Bonferroni correction, and multiple and simple linear

regression analyses were used. We considered $p < 0.05$ to be statistically significant.

Results

The mean age of the 17 patients (7 women, 10 men) enrolled in the study was 60 ± 8 years. Chronic glomerulonephritis was the underlying renal disease in 11 patients, and diabetic nephropathy in 6 patients. During the 5-year study period, 2 patients received once-weekly hemodialysis because of a decrease in weekly creatinine clearance to below 45 L. Parathyroidectomy was performed in 3 patients, and 8 patients were found to have at least 1 enlarged parathyroid gland. We found no direct correlation between levels of intact PTH and the enlarged parathyroid glands detected by ultrasonography (data not shown).

Changes in serum creatinine, Ca, phosphate, intact PTH, and RRF

Figures 1 through 5 show, respectively, the changes in serum creatinine, Ca, phosphate, intact PTH, and RRF in the patients over time. Serum creatinine increased significantly from the start of CAPD to the end of the study ($p < 0.001$). However, serum Ca and phosphate showed no significant changes, with the exception of serum phosphate in the 5th year. Intact PTH gradually increased throughout the study, and from year 1 to year 5, the levels were significantly different. Residual renal function, as evaluated by daily urine volume decreased gradually and, toward the end of the study, significantly (Figure 5). We observed significant correlations (Table I, Figure 6)

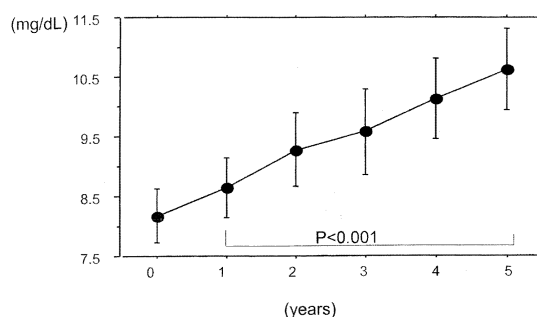


FIGURE 1 Serial changes in serum creatinine over 5 years after the start of continuous ambulatory peritoneal dialysis in new dialysis patients. Serum creatinine increased significantly at year 2 ($p < 0.001$) and continuously thereafter until the end of the study.

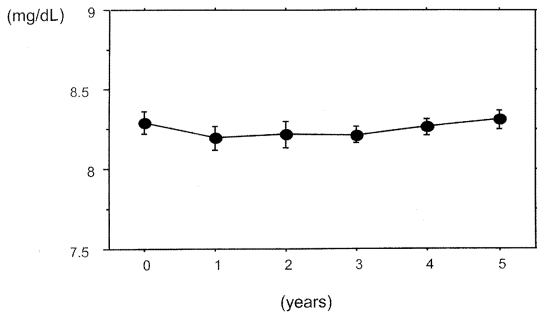


FIGURE 2 Serial changes in serum calcium over 5 years after the start of continuous ambulatory peritoneal dialysis in new dialysis patients. No significant changes were noted throughout the study.

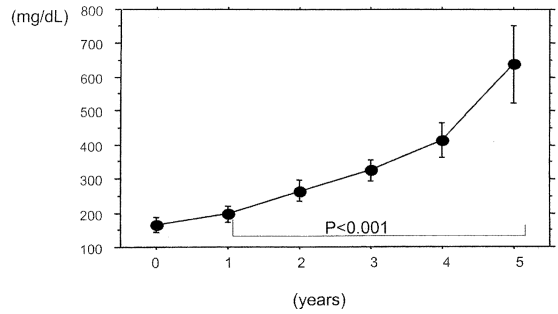


FIGURE 4 Serial changes of serum intact parathyroid hormone (PTH) over 5 years after the start of continuous ambulatory peritoneal dialysis in new dialysis patients. Intact PTH increased significantly at year 2 ($p < 0.001$) and continuously thereafter until the end of the study.

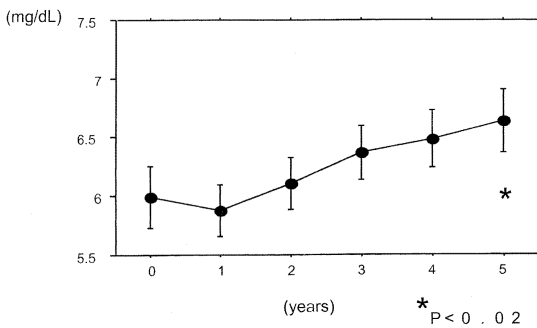


FIGURE 3 Serial changes in serum phosphate over 5 years after the start of continuous ambulatory peritoneal dialysis in new dialysis patients. Serum phosphate increased gradually and continuously starting at year 2 ($p < 0.001$) until the end of the study. At year 5, serum phosphate reached a value that was significantly different from the value at the start of dialysis.

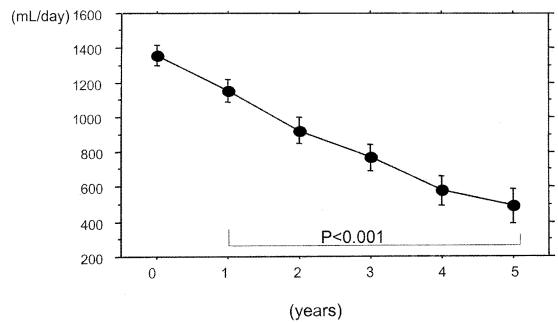


FIGURE 5 Serial changes in urine volume over 5 years after the start of continuous ambulatory peritoneal dialysis in new dialysis patients. Urine volume decreased significantly at year 2 ($p < 0.001$) and continuously thereafter until the end of the study.

between intact PTH and Ca ($p < 0.002$), serum creatinine ($p < 0.02$), and RRF ($p < 0.0001$). After multiple regression analysis, only RRF still correlated significantly with levels of intact PTH.

Discussion

In the present study, the following findings emerged:

- Levels of intact PTH are not always correlated with enlarged parathyroid glands in patients on CAPD.
- Increases in intact PTH correlated significantly with decline in RRF after adjustment in other variables such as serum Ca, phosphate, and creatinine.

Intact PTH in dialysis patients has been reported to be high (6), normal (8), or low (7) by several investigators. Definitive levels remain to be determined and agreed upon.

Levels of PTH are influenced by diet, especially phosphate intake. They are also regulated by serum Ca and are changed by the administration of agents such as phosphate binders and vitamin D analogs. These factors interact in a complex manner in a patient on CAPD, which makes it difficult to determine a “normal level” of intact PTH. Moreover, these factors influence the course of CAPD treatment.

TABLE I Correlations between selected variables in patients on continuous ambulatory peritoneal dialysis

	CRRT	Ca	P	PTH	RRF
CRRT		0.080 (<i>p</i> =0.42)	0.648 (<i>p</i>=0.0001)	0.101 (<i>p</i> =0.31)	0.367 (<i>p</i>=0.0001)
Ca			0.088 (<i>p</i> =0.380)	0.329 (<i>p</i>=0.0007)	0.269 (<i>p</i>=0.006)
P				0.111 (<i>p</i> =0.226)	0.301 (<i>p</i>=0.002)
PTH					0.543 (<i>p</i>=0.0001)
RRF					

CRRT = continuous renal replacement therapy; PTH = intact parathyroid hormone; RRF = residual renal function. Boldfaced *p* values are statistically significant.

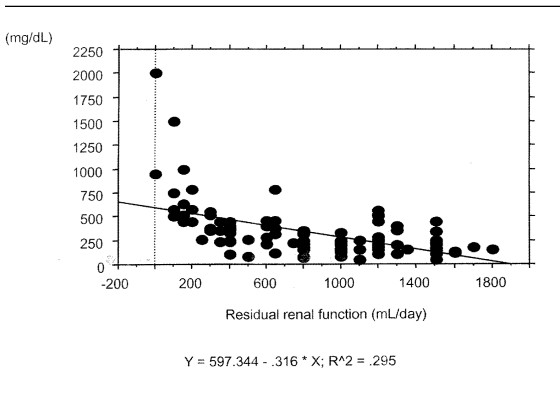


FIGURE 6 Correlation between serum intact parathyroid hormone and urine volume in patients on continuous ambulatory peritoneal dialysis was found to be significant (*p* < 0.01).

The present study clarified the time course of changes in intact PTH in patients on CAPD. Levels of intact PTH increased gradually over 5 years, and 3 patients underwent parathyroidectomy. But despite higher levels of intact PTH, half of the patients enrolled in the present study did not have enlarged parathyroid glands on sonography. The fact that the levels of intact PTH seen in patients on CAPD do not indicate parathyroid tumor suggests the involvement of other factors such as vitamin D levels.

Levels of 25-hydroxyvitamin D3 are usually in the normal range at the start of CAPD, but they begin to decline thereafter (12). This change is not unexpected, because peritoneal dialysis effluent contains significant amounts of vitamin D binding protein, an α_2 -globulin of molecular weight 59 kDa, which binds all three vitamin D

metabolites (1,25-dihydroxyvitamin D3, 25-hydroxyvitamin D3, and 24,25-hydroxyvitamin D3). Losses of 1,25-dihydroxyvitamin D3 and 24,25-hydroxyvitamin D3 have been shown to average approximately 6% – 8% of the plasma pool daily (13). Thus, to bring serum levels of 1,25-dihydroxyvitamin D3 into the normal range, CAPD patients probably require 2 – 3 times the vitamin D maintenance doses used in hemodialysis patients.

In the present study, Ca levels in two thirds of the patients were within normal limits, and vitamin D metabolite was administered to half of the patients. Indeed, hypercalcemia above 10 mg/dL was found in 1 patient, who was treated with vitamin D analog without significant effects. In Japan, sevelamer, a phosphorus binder, was not available until 2003, and therefore, in the present study, no patient received sevelamer for reduction of phosphate levels. We used a Ca-containing binder, and when serum levels of Ca increased above 10 mg/dL, the Ca-containing binder was stopped. In fact, the effect of Ca-containing binder in reducing serum levels of phosphate is rather weak. Levels of serum phosphate in our study patients gradually increased despite the use of the Ca-containing binder.

Intact PTH increased to 2 – 5 times the upper limit of the normal range (between 150 pg/mL and 300 pg/mL) 2 – 3 years after the introduction of CAPD therapy. This increase corresponded with 800 mL of RRF, indicating that, in patients on CAPD, RRF might be important for suppression of PTH. In fact, in a multiple regression analysis, RRF was the only determining factor for PTH. Because sevelamer was not commercially available to our

patients, it is possible that phosphate suppression was unsatisfactory and resulted in increases in PTH levels in combination with decreases in RRF. This hypothesis is supported by finding that hyperphosphatemia stimulates PTH secretion independent of serum Ca level (14,15).

On the other hand, increased phosphate excretion has been shown to result in decreased activity of 25(OH)D-1 α -hydroxylase and, consequently, decreased production of 1,25-dihydroxyvitamin D₃ (16). That decreased production in turn stimulates increased synthesis and secretion of PTH in an attempt to stimulate renal production of 1,25-dihydroxyvitamin D₃. In the present study, we did not measure metabolites of vitamin D₃, and so the influence of vitamin D₃ on the elevation of PTH cannot be evaluated. Further investigation on this matter is needed.

Conclusions

Based on the findings of the present study, we suggest that RRF is an important factor in the regulation of Ca-P metabolism in patients on CAPD.

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