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Secondary Hyperparathyroidism in Severe Chronic Renal Failure Is Corrected by Very-Low Dietary Phosphate Intake and Calcium Carbonate Supplementation

Key Words
Secondary hyperparathyroidism
Dietary phosphorus
Calcium
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Chronic renal failure

Abstract
The main purpose of our study was to verify the effect of a very-low-protein, low-phosphorus diet, supplemented with essential amino acids and keto analogues and with calcium carbonate, on circulating levels of intact parathyroid hormone (i-PTH) in severe chronic renal failure patients with secondary hyperparathyroidism, not treated with any vitamin D preparation. To this aim, we shifted 21 chronic uremics (12 males, 9 females; age 56 ± 13 years) with serum creatinine >6.5 mg/dl and i-PTH >150 pg/ml, from a standard low-protein diet (0.6 g/kg/day approximately) to a very-low-protein (0.3 g/kg/day), very-low-phosphorus (5 mg/kg/day) diet supplemented with a mixture of essential amino acids and calcium keto analogues (Ketodiet), calcium carbonate (2–4 g/day), iron, and vitamin B_{12} preparations. The energy supply of both diets was 30–35 kcal/kg/day. Exclusion criteria were a poor compliance with dietary or supplement prescriptions or signs of autonomic hyperparathyroidism. After 4 ± 2 months of Ketodiet, the i-PTH serum levels decreased by 49% as a mean (from 441 ± 233 to 225 ± 161 pg/ml, $p < 0.001$); serum phosphorus and alkaline phosphatase decreased, whereas serum calcium increased. The great reduction of serum and urinary urea demonstrated a good compliance with Ketodiet, and no sign of protein malnutrition was observed. These findings confirm that even in severe chronic uremic patients dietary phosphorus restriction and calcium carbonate supplementation lower i-PTH serum levels. This is one of the goals of the dietary treatment that can be safely achieved, provided good compliance both with the dietary prescriptions and with adequate energy and supplement intakes.

Introduction

Secondary hyperparathyroidism is a common and severe complication of chronic renal failure, causing negative effects on bone metabolism and structure and other systemic disturbances. Therefore, the prevention and the treatment of secondary hyperparathyroidism must be regarded as a major goal in the conservative management of chronic uremics. It is known that hyperphosphatemia elicits parathyroid hormone (PTH) synthesis and secre-

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Table 1. Underlying renal disease of the patients studied

Disease	n
Glomerulonephritis	6
Tubulointerstitial nephritis	2
Polycystic kidney disease	3
Diabetic nephropathy	2
Renal vascular nephropathy	2
Unknown	6

Table 2. Composition of the Ketodiet and of the supplements

Diet	
Energy	30–35 kcal/kg per day
Carbohydrates	65%
Lipids	30%
Proteins	4%
Supplements	
Calcium carbonate	2–4 g daily
Vitamin B_{12}	1,000 U weekly
Amino acids and keto acids[a]	1 tablet/5 kg b.w.

[a] Composition (mg) of the essential amino acid and keto acid tablet: l-lysine 105, l-threonine 53, l-tyrosine 30, l-histidine 38, Ca ketovaline 86, Ca ketoleucine 101, Ca ketoisoleucine 67, Ca ketophenylalanine 68, Ca OH-methionine 59.

tion, and that a similar effect is exerted by low serum concentrations of ionized calcium and 1,25-$(OH)_2D_3$ [1, 2]. It is well known that calcitriol reduces PTH synthesis and parathyroid cell proliferation [2, 3], but these beneficial effects can be counteracted by its action on intestinal phosphate absorption.

Therefore, correction of hyperphosphatemia and hypocalcemia by lowering dietary phosphorus intake and by the administration of calcium-containing phosphate binders is the first target of therapeutic intervention [4], whereas the use of vitamin D derivatives is questionable, in predialysis patients at least [5].

The favorable effect of severe dietary phosphorus restriction and calcium supplementation on intact PTH (i-PTH) serum levels in predialysis patients has been previously demonstrated, but native vitamin D was also employed [6, 7].

The aim of the present study has been to verify what can be obtained through dietary manipulation and calcium carbonate supplementation independent of vitamin D administration. In our opinion, the indiscriminate use of vitamin D in patients with a very poor residual renal function can worsen the control of phosphatemia and enhance the risk of hypercalcemia and of soft-tissue calcifications. Therefore, we have studied the effects of a very-low-protein, low-phosphorus diet, supplemented with essential amino acids and ketoanalogues and calcium carbonate, on i-PTH serum levels in severe chronic renal failure patients with secondary hyperparathyroidism, not treated with any vitamin D preparation.

Patients and Methods

Twenty-one chronic uremic patients (12 males, 9 females, age 56 ± 13 years) with serum creatinine >6.5 mg/dl and i-PTH serum levels >150 pg/ml were selected. At the entry of the study, all patients were following a standard low-protein diet, providing approximately 0.6 g/kg/day of proteins and 9–10 mg/kg/day of phosphorus. Treatment with Vitamin D preparations, and clinical or biochemical signs of autonomic hyperparathyroidism were considered exclusion criteria. Also patients showing poor compliance with dietary prescriptions, checked through the determination of the protein catabolic rate according to the formula of Maroni et al. [8], were excluded.

The underlying renal disease of selected patients is reported in table 1. No hypertrophic parathyroid glands were detected by neck ultrasound tomography.

According to the poor residual renal function, all patients were shifted to a very low-protein (0.3 g/kg/day, plant source only), very-low-phosphorus (5–6 mg/kg/day) diet supplemented with essential amino acids and calcium keto acids (Ketodiet). The mixture of amino acids and keto acids (Alfa-Kappa®; Farmabiagini, Italy) was given at the dosage of 1 tablet per 5 kg body weight. Calcium carbonate was given at daily doses of 2–4 g. Since each Alfa-Kappa tablet provides 50 mg of elemental calcium and since the dietary content is approximately 300 mg, the estimated total calcium intake varies from 1.6 to 2.5 g daily, i.e., 2 g as a mean. Iron and vitamin B_{12} preparations were also administered. The compositions of the Ketodiet and of the supplements are shown in table 2. Neither aluminum-containing phosphate binders nor vitamin D preparations were given. During the study period no patient received recombinant erythropoietin.

At baseline and after 2–6 months of Ketodiet, plasma creatinine, creatinine clearance, plasma and urinary urea, i-PTH, plasma calcium, inorganic phosphorus, total and high-density lipoprotein cholesterol, triglycerides, apolipoproteins A1 and B, serum total protein, and serum albumin were measured by the standard procedures employed in our laboratory.

The i-PTH serum levels were determined using an immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, Calif., USA), with normal values ranging from 10 to 60 pg/ml.

All results are reported as mean values ± SD. Statistical evaluation has been performed by Student's t test for paired data. The differences were regarded as statistically significant when $p < 0.05$.

Results

After 4 ± 2 months of Ketodiet, i-PTH serum levels decreased by 48% as a mean, i.e., from 433 ± 233 to 225 ± 161 pg/ml ($p < 0.001$, table 3).

In 4 out of the 21 patients the i-PTH serum levels fell under 80 pg/ml.

Plasma inorganic phosphorus decreased, whereas total calcium increased (table 3). No patient experienced hypercalcemia (plasma total calcium >10.5 mg/dl). The plasma magnesium concentration did not change, whereas serum alkaline phosphatase and calcium-phosphate product significantly decreased (table 3). The data regarding the other parameters studied are reported in table 4.

At the end of the follow-up period, the creatinine clearance was slightly but significantly reduced. Serum urea levels, urinary urea daily excretion, and protein catabolic rate were much lower during the Ketodiet, according to a good compliance with the prescribed protein intake. In our series no sign of protein malnutrition was observed (table 4).

As far as the lipid pattern is concerned, a significant reduction of apolipoprotein B has been observed, without any significant change of cholesterol or triglyceride plasma levels (table 4).

Table 3. Changes of serum levels of i-PTH, total calcium, phosphorus, magnesium, and alkaline phosphatase in the studied uremic patients shifted from a low-protein diet to the Ketodiet

	Baseline	Ketodiet	p
i-PTH, pg/ml	441±233	225±161	<0.001
Calcium, mg/dl	8.3±0.8	8.9±0.6	<0.001
Phosphorus, mg/dl	5.0±1.0	3.7±0.9	<0.001
Magnesium, mEq/l	2.1±0.5	2.2±0.4	n.s.
Alkaline phosphatase, U/l	246±70	205±72	<0.01
Calcium × phosphate product	41±9	34±8	<0.001

n.s. = Not significant.

Table 4. Renal function, body weight, protein catabolic rate, urinary urea, and other blood biochemistry data in the patients studied before and during the ketoacid diet

	Baseline	Ketodiet	p
Plasma creatinine, mg/dl	7.9±1.3	8.1±1.4	n.s.
Creatinine clearance, ml/min	7.2±3.3	5.6±2.4	<0.001
Plasma urea, mg/dl	126±29	63±21	<0.001
Urinary urea, g/24 h	6.8±2.5	2.7±0.9	<0.001
Total protein, g/dl	6.7±0.5	6.5±0.4	n.s.
Albumin, g/dl	4.0±0.4	3.8±0.4	n.s.
Total cholesterol, mg/dl	195±55	181±56	n.s
HDL cholesterol, mg/dl	35±10	36±10	n.s.
LDL cholesterol, mg/dl	125±47	118±48	n.s.
Triglycerides, mg/dl	157±102	152±93	n.s.
Apolipoprotein A1, mg/dl	133±23	142±28	n.s.
Apolipoprotein B, mg/dl	119±45	97±32	<0.01
Hemoglobin, g/dl	9.8±1.5	9.3±1.3	n.s.
Hematocrit, %	29.1±4.6	28.1±4.1	n.s.
PCR, g/kg/day	0.50±0.10	0.32±0.05	<0.001
Body weight, kg	69.2±13.0	68.1±13.4	n.s.

n.s. = Not significant; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PCR = protein catabolic rate.

Discussion

Our data demonstrate that the Ketodiet reduces i-PTH serum levels in severe chronic renal failure patients on conservative treatment, irrespective of any vitamin D administration. These results confirm our previous observations of a similar effect exerted by dietary treatment on circulating NH_2- and C-terminal PTH fragments [4]. More recently, Lafage et al. [6] and Combe and Aparicio [7] demonstrated the reversal of secondary hyperparathyroidism and some favorable effects on bone metabolism exerted by a similar dietary regimen associated with native vitamin D administration. Of course, also those results were achieved on the basis of a good compliance with dietary phosphorus restriction and with supplement intake.

In our practice, when the conservative treatment with very low-protein diets is correctly performed, the risk of protein and energy malnutrition is negligible [9], as clearly demonstrated in recent studies [10, 11]. However, because of the severity of protein and phosphorus restrictions, these dietary regimens are often difficult to perform. Thereby strong motivation and involvement are needed both by the patients and by the physicians. Unfortunately this does not always occur [12].

Despite the severe reduction of the residual renal function of our patients at the beginning of the study, the plasma phosphate levels decreased during the Ketodiet. This effect is accounted for the reduced intestinal phosphate uptake due to the very low dietary phosphorus content

and to the phosphate-binding action of calcium supplied with keto acids and with carbonate.

Our results are in keeping with the key role of dietary phosphate restriction as prevention and treatment of secondary hyperparathyroidism [13, 14]. Data from the literature have clearly demonstrated a direct effect of phosphorus restriction on parathyroid gland function and growth in chronic renal failure, independently of calcium and of calcitriol changes [2, 15].

Although phosphate restriction could increase endogenous calcitriol production and in turn contribute to lower PTH secretion, this mechanism seems quite unlikely in our series. Data from the literature demonstrate that only in the early stages of renal failure calcitriol serum levels can be increased by dietary phosphorus restriction. Instead, when the residual renal function is very poor, as in our patients studied, calcitriol serum levels cannot be modulated by dietary management [16, 17].

It is well known that intestinal calcium absorption does not entirely depend on calcitriol, but it also occurs when a positive intestinal transluminal gradient for calcium ions is created. This is the reason why a relatively high calcium intake has been prescribed in our patients untreated with any vitamin D derivatives. Therefore, calcium salt supplementation can increase calcium plasma levels even in the absence of vitamin D administration, avoid a negative calcium balance, and bind intestinal phosphate. The increase of calcium plasma levels can be favored also by the decrease of phosphatemia: both conditions contribute to reduced PTH synthesis and secretion.

Moreover, it is to notice that the calcium supplied with the keto acids is very important because it has an effective phosphate binder action even when the gastric acidification is impaired [18].

In the present study, no vitamin D preparation was given with the aim to evaluate the effect of dietary restrictions and calcium supplementation independent of any vitamin D administration and because of its potential disadvantages despite the described favorable effects of calcitriol on PTH synthesis and parathyroid cell proliferation [2].

In fact, calcitriol increases intestinal phosphate absorption, thereby counteracting the hypophosphatemic effect of dietary restriction and of calcium-containing phosphate binders. It increases calcium absorption and in turn the risks of hypercalcemia, high calcium-phosphate product, and soft-tissue calcifications. If this is the case, aluminum-containing phosphate binder administration could be necessary, hence exposing the patients to the hazards of aluminum intoxication.

The quite high calcium intake we recommended could be of some concerns about the risk of soft tissue calcifications and of favoring the progression of renal damage. Calcium salt precipitation in the kidney can contribute to the progression of renal damage when hypercalcemia occurs or when high-normal plasma calcium levels are associated with hyperphosphatemia as, for instance, when high calcium doses are given together with calcitriol.

Conversely, it is well known that phosphorus restriction and correction of hyperparathyroidism lower the calcium renal content and protect the residual renal function in the remnant kidney model. The calcium supplementation together with dietary phosphorus restriction, in the absence of vitamin D administration, only slightly increases calcium plasma levels. In addition, it reduces phosphatemia and calcium-phosphate product, then preventing or correcting secondary hyperparathyroidism; these changes are able to protect, instead of to worsen, the residual renal function.

In a few patients i-PTH was oversuppressed, and then we reduced the amount of calcium carbonate supplementation. This demonstrates that in those patients the treatment we proposed was more than enough and supports the therapeutic advice to avoid the indiscriminate use of vitamin D because it could further increase the risk of low turnover bone disease. The use of low doses of calcitriol can be proposed in selected patients unresponsive to the dietary phosphorus restriction and calcium supplementation.

The vegetarian diet and calcium carbonate [19] can potentially ameliorate the lipid pattern. However, only the apolipoprotein B plasma levels were significantly reduced. The absence of important lipid abnormalities at baseline could probably account for these data.

In summary, our findings confirm that a significant reduction of serum i-PTH levels can be achieved even in severe chronic renal failure by dietary phosphorus restriction and calcium supplementation. This is one of the purposes of the dietary conservative management that can be safely and quite easily obtained, provided good compliance with both the severe dietary restrictions and an adequate energy and supplements intake. Calcitriol could represent a further therapeutic tool in the patients with unsatisfactory reduction of i-PTH levels, provided careful monitoring of phosphate and of calcium plasma levels. In our opinion, in predialysis patients at least, the adequacy of dietary protein and phosphorus restrictions to the residual renal function and calcium carbonate supplementation represent the basis of the treatment of the secondary hyperparathyroidism. Calcitriol administration

could be taken into account and carefully employed in the cases with incomplete PTH reduction, provided good control of phosphatemia is obtained through dietary phosphorus restriction.

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