Phosphorus restriction reverses hyperparathyroidism in uremia independent of changes in calcium and calcitriol

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LOPEZ-HILKER, SILVIA, ADRIANA S. DUSSO, NEVILLE S. RAPP, KEVIN J. MARTIN, AND EDUARDO SLATOPOLSKY. *Phosphorus restriction reverses hyperparathyroidism in uremia independent of changes in calcium and calcitriol.* Am. J. Physiol. 259 (Renal Fluid Electrolyte Physiol. 28): F432–F437, 1990.—Phosphorus is a well-known modulator of renal 1α-hydroxylase activity. In early and moderate renal failure it is proposed that dietary P_i reduction ameliorates secondary hyperparathyroidism through increased circulating levels of calcitriol (i.e, 1α,25-dihydroxycholecalciferol). To gain further insight into the mechanisms by which a low-P_i diet ameliorates secondary hyperparathyroidism in advanced renal insufficiency, studies were performed in five dogs before and 6 mo after the induction of uremia by 5/6 nephrectomy. Glomerular filtration rate decreased from 69.0 ± 2.3 to 10.5 ± 0.5 ml/min, immunoreactive parathyroid hormone (irPTH) increased from 66.0 ± 8.8 to 321.0 ± 46 pg/ml, and calcitriol decreased from 39.0 ± 10.4 to 27.0 ± 6.2 pg/ml. Thereafter, dietary P_i was decreased gradually every 2 wk from 0.95% to 0.6, 0.45, and 0.3%, respectively. Dietary Ca was reduced from 1.6 to 0.6% to prevent development of hypercalcemia. Ionized Ca (ICa) decreased from 5.4 ± 0.04 to 5.2 ± 0.05 mg/dl ($P < 0.02$), and plasma P_i decreased from 6.3 ± 0.7 to 4.7 ± 0.2 mg/dl ($P < 0.05$). Calcitriol remained low (23.3 ± 4.7 pg/ml). However, irPTH gradually decreased from 321.0 ± 46.0 to 94.7 ± 22.9 pg/ml ($P < 0.005$). These studies indicate that a decrease in dietary P_i from 0.95 to 0.3% suppressed irPTH by ~70%. Reduction of irPTH was observed in the absence of a concomitant increase in levels of ICa or calcitriol. These studies suggest that reduction in dietary P_i in advanced renal insufficiency improves secondary hyperparathyroidism by a mechanism that is independent of the levels of calcitriol or plasma ICa.

calcitriol; uremia; vitamin D; phosphorus retention

RENAL INSUFFICIENCY is characterized by several alterations in mineral homeostasis. Secondary hyperparathyroidism is present even in the early stages of renal insufficiency and leads to the development of renal osteodystrophy (17, 22, 31, 32, 37, 38).

The two major pathogenetic mechanisms responsible for the development of secondary hyperparathyroidism in advanced renal insufficiency are phosphorus retention and low levels of calcitriol (i.e., 1α,25-dihydroxycholecalciferol). Hyperphosphatemia results in hypocalcemia by several possible mechanisms, including inhibition of the activity of the renal enzyme 1α-hydroxylase (36), which is already limited by the decrease in renal mass. Low levels of calcitriol lead to decreased calcium transport by the gastrointestinal tract (4), altered synthesis (30) and secretion (3, 21, 34) of parathyroid hormone (PTH), and possibly skeletal resistance to the calcemic action of PTH (18, 19, 35).

Support for the major role of phosphorus retention (1, 33) has been provided by several investigators who have shown that decreasing the amount of phosphorus in the diet in proportion to the fall in glomerular filtration rate (GFR) prevents (32) or ameliorates (11, 14, 23) secondary hyperparathyroidism. The mechanism of this effect remains unclear. In normal humans (25) and in patients with moderate renal insufficiency (14, 23), restriction of dietary phosphorus increases the production of calcitriol, thus decreasing the levels of immunoreactive (ir) PTH. However, this mechanism may not be operative in advanced renal insufficiency, because the decrease in renal mass may severely limit the production of calcitriol.

The present studies were designed to determine if the effect of dietary phosphorus restriction on PTH secretion in advanced renal failure could be dissociated from changes in the well-established regulators of PTH secretion, calcium, and calcitriol.

METHODS

Five female mongrel dogs were studied. Initially, all five normal dogs were fed 400 g/day of Purina High-Pro dog diet, which provided 1.6% calcium and 0.95% phosphorus. After completion of baseline studies [GFR, plasma irPTH, calcitriol, ionized calcium (ICa), and phosphorus] experimental renal insufficiency was induced by 5/6 nephrectomy. This was achieved by ligation of all but one of the terminal branches of the left renal artery and, 10–15 days later, by right contralateral nephrectomy as previously described (32). After 23 wk of experimental renal insufficiency the diet was changed to a "low-calcium, low-phosphorus diet" (0.3 and 0.02%, respectively; ICN Biomedical, Cleveland, OH) supplemented with a daily total of 1.6% calcium and 0.95% phosphorus similar to the amount ingested with the Purina dog chow diet. After 3 wk of equilibration on this diet, GFR and baseline plasma samples were obtained. Thereafter, dietary phosphorus was progressively decreased every 2 wk from 0.95% to 0.6, 0.45, and 0.3% (Fig. 1). To prevent the development of hypercalcemia, dietary calcium intake was decreased from 1.6 to 0.6%

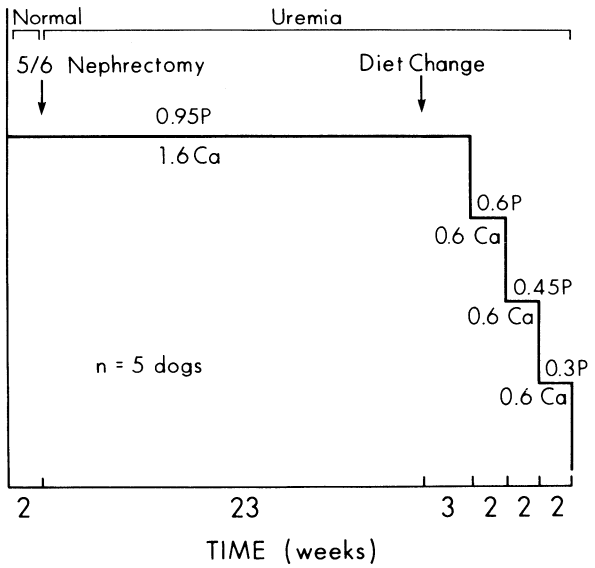

FIG. 1. Depiction of the protocol involving dietary phosphorus and calcium manipulation before and after 5/6 nephrectomy in 5 adult female mongrel dogs. *Left arrow*, induction of experimental renal insufficiency; *right arrow*, time when diet was changed.

when dietary phosphorus reduction was initiated. Thereafter, calcium intake was maintained constant throughout the studies. The diet was administered twice daily by gastric intubation and provided a total caloric intake of 1880 calories. Blood samples were obtained at 8:00 A.M. twice weekly for the determination of ICa, phosphorus, creatinine, NH_2-terminal irPTH, and calcitriol.

To investigate the acute effect of the ingestion of a low-phosphorus diet on plasma ICa, three uremic dogs were studied. After the collection of four blood samples (control samples), 0.45% phosphorus and 0.6% calcium as an oral diet load (200 g) was administered by gastric intubation. Blood samples were collected at 30, 60, and 90 min and thereafter at 2, 3, 4, 5, 6, 7, 8, 12, and 24 h postload.

Analytical methods. Plasma ICa was measured by an ionized-calcium-specific electrode (model ICA-1; Radiometer, Copenhagen). Plasma phosphorus was determined by a Multistat III Plus (Instrumentation Laboratory). Exogenous creatinine clearance was used to determine GFR (33). irPTH was determined in normal and uremic animals by a radioimmunoassay developed in our laboratory, with specificity for the NH_2-terminal region of the PTH molecule. The characteristics of this assay have been described previously (15). All samples from each dog were determined in either duplicate or quadruplicate within the same assay. Intra-assay variation was 8%, and interassay variation was 9%. Calcitriol levels were measured in 1-ml plasma samples extracted after the procedure developed by Hollis (10). The calcitriol fraction was quantitated by radio receptor assay as described by Reinhardt et al. (26). Intra-assay variation was 6.2%, and interassay variation was 11.4%.

The results are expressed as means ± SE. Paired *t* test or analysis of variance was used to quantitate statistical differences with treatment.

RESULTS

Acute effect of 0.45% dietary phosphorus on plasma ICa in uremic dogs. To investigate the acute effect of the ingestion of a low-phosphorus diet on plasma ICa, three uremic dogs were studied. After the oral administration of the diet containing 0.45% phosphorus, plasma ICa levels did not change significantly (Fig. 2).

Effect of uremia on GFR, calcium, phosphorus, irPTH, and calcitriol. During control studies the GFR was 69.4 ± 2.3 ml/min. The dogs were then rendered uremic, and after 5.3 ± 0.3 mo of renal failure the GFR was 10.5 ± 0.5 ml/min (85.0 ± 0.7% reduction in GFR, $P < 0.005$). Figure 3 illustrates the effect of the experimental induction of renal insufficiency on plasma ICa, phosphorus, irPTH, and calcitriol. After 5.3 ± 0.3 mo of experimental

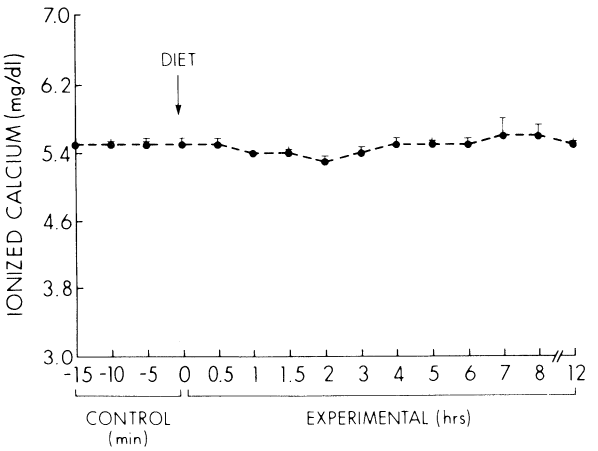

FIG. 2. Acute effect of 0.45% dietary phosphorus load on plasma ionized calcium in uremic dogs.

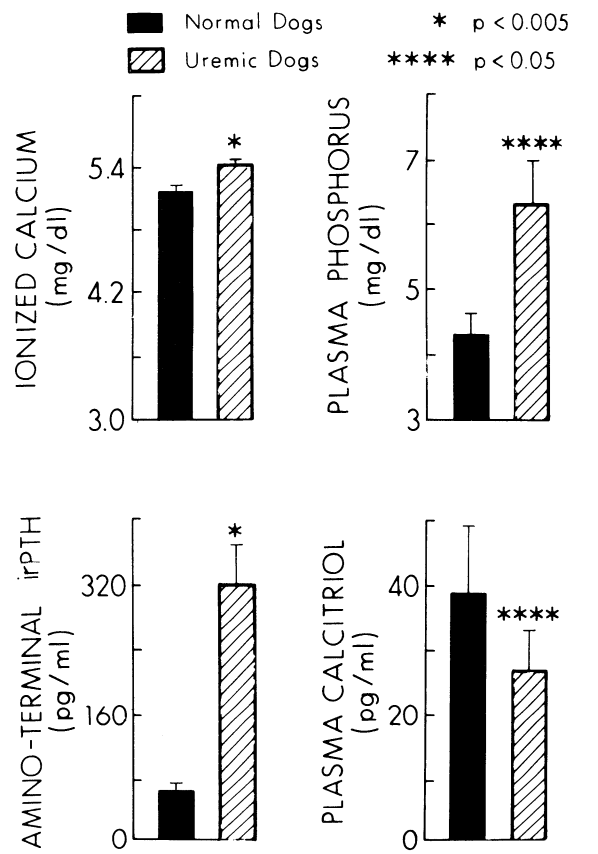

FIG. 3. Effects of uremia on plasma ionized calcium and phosphorus (*top*) and NH_2-terminal immunoreactive parathyroid hormone (irPTH) and calcitriol (*bottom*).

renal insufficiency and the administration of a high-calcium diet (1.6%) a significant increase in plasma ICa levels from 5.16 ± 0.07 to 5.43 ± 0.04 mg/dl ($P < 0.005$) was observed. As expected, plasma phosphorus increased from 4.2 ± 0.3 to 6.3 ± 0.7 mg/dl ($P < 0.05$). Despite a significant increase in plasma ICa, each animal developed severe secondary hyperparathyroidism. Mean irPTH increased from 65.9 ± 8.9 to 320.8 ± 46.3 pg/ml ($P < 0.005$). A significant fall in plasma calcitriol levels from 39.2 ± 10.4 to 27.0 ± 6.2 pg/ml ($P < 0.05$) was also observed. These results are similar to data obtained by us previously (15).

Effect of dietary phosphorus on plasma ICa, phosphorus, and irPTH in uremic dogs. Figure 4 depicts the effect of a progressive decrease in dietary phosphorus on plasma ICa, phosphorus, and irPTH in uremic dogs. The decrease in dietary phosphorus from 0.95 to 0.6% and in dietary calcium from 1.6 to 0.6% produced a small but significant fall in ICa levels (Fig. 4, *top*), from 5.43 ± 0.04 to 5.2 ± 0.05 mg/dl ($P < 0.02$). When phosphorus was further reduced to 0.45%, ICa remained lower on this diet. With the administration of 0.3% dietary phosphorus, plasma ICa was not different from the value obtained when the uremic animals were receiving 0.95% dietary phosphorus. Plasma phosphorus concentration (Fig. 4, *middle*) decreased from 6.3 ± 0.7 to 4.7 ± 0.2 mg/dl ($P < 0.05$) when dietary phosphorus was reduced to 0.6%. A further decrease in dietary phosphorus to 0.45 and 0.3% maintained plasma phosphorus levels within normal limits. The absence of a further decrease in plasma phosphorus concentrations, despite the progressive decrease in dietary phosphorus, may be due to the significant reduction in renal mass (>85%). Interestingly, despite the reduction in plasma ICa concentration, irPTH levels (Fig. 4, *bottom*) decreased from 320.8 ± 46.3 to 145.6 ± 28.4 pg/ml ($P < 0.02$) when the animals were fed 0.6% dietary phosphorus. The administration of 0.3% dietary phosphorus produced a further reduction in irPTH levels to 94.7 ± 22.9 ($P < 0.01$). These latter values are not different from those observed when the animals were normal. A significant correlation between plasma phosphorus and NH_2-terminal irPTH was observed ($r = 0.4$, $P < 0.001$, $n = 33$).

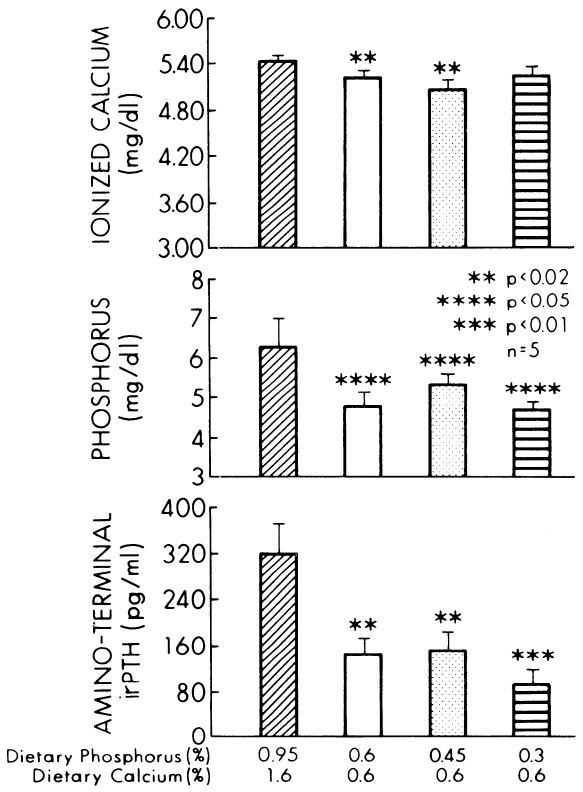

FIG. 4. Effects of dietary phosphorus on plasma ionized calcium (*top*), plasma phosphorus (*middle*), and NH_2-terminal immunoreactive PTH (irPTH) (*bottom*) in 5 uremic female dogs.

Effect of dietary phosphorus on plasma calcitriol in uremic dogs. Reduction of dietary phosphorus from 0.95 to 0.6% did not affect the levels of plasma calcitriol, 27.0 ± 6.2 vs. 26.7 ± 5.5 pg/ml, respectively (Fig. 5). Despite the further progressive dietary phosphorus restriction to 0.3%, plasma calcitriol concentration did not increase (23.3 ± 4.7 pg/ml, NS).

Correlation between plasma calcitriol and plasma creatinine. Plasma calcitriol correlated inversely and significantly with plasma creatinine ($r = -0.52$; $P < 0.001$, $n = 35$) (Fig. 6). The plasma concentration of calcitriol did not correlate with either changes in PTH or in plasma phosphorus.

DISCUSSION

The in vivo effects of dietary phosphorus on calcitriol synthesis in normal volunteers and in patients with early and moderate renal insufficiency have been studied in detail. In healthy humans, Portale et al. (25) found that, when dietary phosphorus was restricted and then supplemented, an increase and then a decrease in plasma calcitriol was observed. This phenomenon was associated with an increase and decrease in the production rate of calcitriol, respectively, with no change in metabolic clearance rate. Recently (24) the same investigators clearly demonstrated that, in normal men dietary phosphorus can finely regulate the serum concentration of calcitriol, and this regulation is mediated by the serum concentration of phosphorus. Gray et al. (9) also demonstrated in healthy women an increase in calcitriol levels in response to dietary phosphorus restriction. In patients with moderate renal insufficiency (14, 23), despite no changes in plasma phosphorus concentrations, dietary phosphorus restriction produced a significant increase in plasma calcitriol with a concomitant normalization of plasma irPTH concentration. Improvement in the calcemic response to irPTH extract and in intestinal calcium absorption was also demonstrated (14). Because the circulating concentration of irPTH varied inversely with that of calcitriol, it was concluded that the decrease in plasma PTH concentration was due to an increase in calcitriol levels.

Because in advanced renal insufficiency the reduced renal mass may limit the production of calcitriol, the present studies were performed to clarify the mechanism by which dietary phosphorus restriction improves secondary hyperparathyroidism in advanced renal insufficiency. Thus we examined whether dietary phosphorus restriction would produce an increase in calcitriol syn-

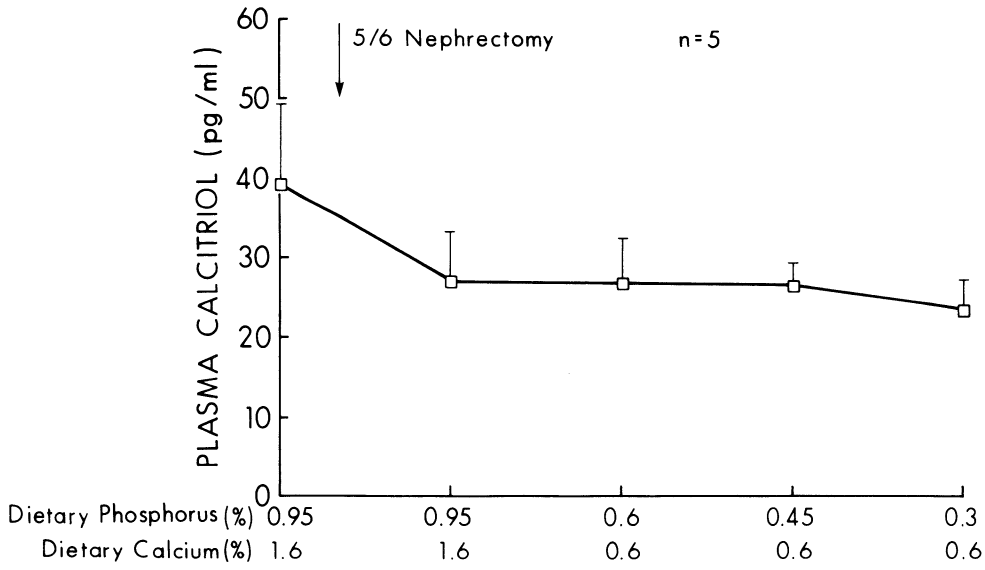

FIG. 5. Effects of dietary calcium and phosphorus on plasma calcitriol in 5 uremic female dogs. *Arrow*, induction of renal failure.

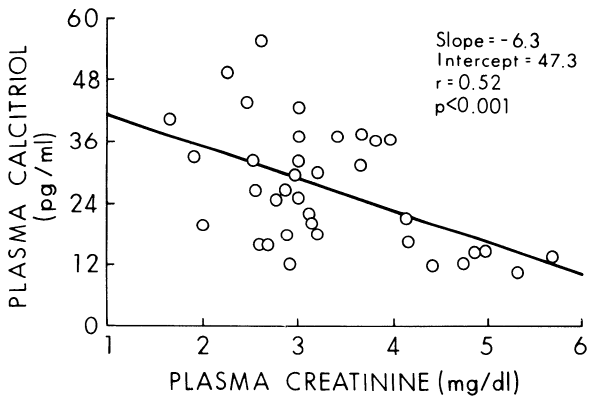

FIG. 6. Correlation of plasma calcitriol and plasma creatinine in 5 uremic female dogs.

thesis in advanced renal insufficiency (GFR < 10.5 ml/min) similar to that observed in early and moderate renal insufficiency. The results confirm a dramatic effect of phosphorus restriction in secondary hyperparathyroidism. However, in contrast to previous findings in patients with early renal insufficiency, in the dogs with advanced renal insufficiency progressive reduction in dietary phosphorus to 0.3% did not increase plasma calcitriol levels (Fig. 5). In humans and rats, calcium and phosphorus are well-known modulators of the renal 1α-hydroxylase activity. In the present studies, we observed a significant reduction in plasma ICa and phosphorus levels (Fig. 4), conditions known to stimulate the renal 1α-hydroxylase, but plasma calcitriol concentration did not increase. Plasma calcitriol levels varied in indirect proportion to plasma creatinine ($P < 0.001$) (Fig. 6), suggesting that in advanced renal insufficiency the reduced renal tissue mass is a major determinant of calcitriol synthesis and/or secretion. In phosphorus-deprived rats, in vitro calcitriol synthesis was a linear function of the wet weight of tissue slices (8). Thus, in advanced renal failure, the significant decrease in renal mass may not allow dietary phosphorus restriction to increase calcitriol synthesis (Fig. 5).

Although phosphorus restriction may cause hypercalcemia, the present studies show that hypercalcemia was not responsible for the decrease in irPTH levels, since a significant reduction in ICa levels was observed when dietary phosphorus was reduced to 0.6% and then to 0.45% (Fig. 4). Probably the decrease in plasma ICa was secondary to a concomitant reduction in dietary calcium from 1.6 to 0.6%. The fact that plasma ICa concentration did not increase in the immediate hours post-feeding would seem to eliminate this as a factor responsible for the decrease in NH_2-terminal irPTH (Fig. 2). The restriction in dietary phosphorus decreased plasma phosphorus toward normal values; however, despite further reduction in dietary phosphorus to 0.3%, plasma phosphorus levels did not continue to decrease (Fig. 4). Intracellular phosphorus content of kidney cortical cells is a major control mechanism for the renal 1α-hydroxylation of 25-hydroxyvitamin D or calcidiol (36). Although Gray et al. (7) did not find any change in total or acid-soluble renal cortical phosphate content in normal rats after 4 days of dietary phosphorus restriction, it is possible that, in advanced renal insufficiency where hyperphosphatemia is usually present, small and specific intracellular phosphate pools may be at least partially responsible for the lack of response of plasma calcitriol to dietary phosphorus restriction.

In agreement with our results, Lucas et al. (16) found that, despite the administration of a low-phosphorus diet to patients with advanced renal insufficiency (GFR < 10 ml/min), not only did plasma calcitriol levels not increase, but a significant decrease was demonstrated. Plasma concentration of intact PTH and plasma phosphorus levels significantly decreased, and no change in total calcium was observed. Unfortunately, these patients were receiving phosphate binders containing aluminum. It has been demonstrated in vivo (13) and in vitro (20) that aluminum can inhibit PTH secretion. Thus clear understanding of the effect of dietary phosphorus restriction on PTH secretion was not possible from this study. Recently, Schaefer et al. (28) obtained similar results in a group of 17 patients with advanced renal insufficiency (plasma creatinine 8.5 mg/dl) by adding keto acid to their diets. After 8 wk of treatment they

found a significant decrease in the levels of plasma phosphorus and irPTH. There were no changes in plasma calcium, calcitriol, or 25-hydroxyvitamin D. Tessitore et al. (37) showed that, at a GFR of <20 ml/min, dietary phosphorus restriction did not have any effect on calcitriol concentration. In vitamin D-deficient rats, Dabbagh et al. (5) observed that, in the presence of a normal plasma calcium concentration, the administration of a phosphorus-restricted diet prevented the development of secondary hyperparathyroidism. Thus, not only in humans (16, 28) but also in dogs (this study) and in rats (5), phosphorus restriction is associated with suppression of PTH secretion, an effect that is independent of the levels of calcitriol.

Contrary to the classical theory that hypocalcemia plays a major role in the genesis of secondary hyperparathyroidism in renal insufficiency, in the present studies when the dogs were rendered uremic, despite a significant rise in plasma ICa concentration (Fig. 3), severe secondary hyperparathyroidism developed. These results are in agreement with previous findings from our laboratory (15) and from other investigators (22). In our previous studies, when the decrease in calcitriol concentration (15) was prevented by the administration of a physiological dose of calcitriol, the animals did not develop secondary hyperparathyroidism. In the past decade numerous investigators have demonstrated a direct suppressive effect of calcitriol on PTH release (2, 3). It has also been shown that calcitriol decreases steady-state levels of prepro-PTH RNA in a dose-dependent manner. Moreover, Silver et al. (29) and Russell et al. (27) demonstrated that calcitriol plays an important role in the regulation of PTH gene transcription. Our own laboratory has presented convincing evidence for the action of calcitriol on PTH secretion (3, 6, 15, 34). Thus currently there is full agreement between investigators on the critical role of calcitriol on the regulation of PTH secretion. The results obtained in this study do not minimize the importance of calcitriol in the regulation of PTH. These findings imply an additional important role for phosphorus in the control of irPTH secretion by a mechanism which is independent of the levels of calcitriol or plasma ICa.

In conclusion, dietary phosphorus restriction corrected secondary hyperparathyroidism in dogs with advanced renal insufficiency. This effect was not mediated by increased levels of calcitriol or plasma ICa. Thus, in addition to the well-known effects of phosphorus in the regulation of calcitriol, a low-phosphorus diet may have an effect on the secretion of PTH. Although the mechanism of this effect is not yet known, potentially phosphorus may affect phospholipid composition of the parathyroid cell membrane, calcium fluxes in the parathyroid cells, and/or regulation of calcitriol receptors in the parathyroid cell (12). Thus phosphorus may indirectly regulate the secretion of PTH. Further studies are necessary to determine the precise mechanism by which phosphorus contributes to the regulation of PTH secretion in chronic renal failure.

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