Effect of Phosphate Depletion on Magnesium Homeostasis in Rats

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ABSTRACT The effects of phosphate depletion on magnesium (Mg) homeostasis were evaluated in rats fed a diet containing 0.03% phosphorus for periods up to 8 wk. Plasma phosphorus fell significantly ($P < 0.01$) from 10.1±0.27 (SE) to 5.0±0.54 mg/100 ml within 1 day and continued to fall gradually to a level of 1.2±0.21 mg/100 ml by the end of the 8th wk. A significant ($P < 0.01$) increment in urinary Mg excretion (UMgV) from 46±2.7 to 126±24 μeq/24 h occurred during the 1st day of phosphate depletion; UMgV reached a peak of 300±24 μeq/24 h by the 3rd day and remained high ranging between 150–300 μeq/24 h, thereafter. The magnitude of the magnesuria was related to the degree of hypophosphatemia and was not affected by lowering the calcium intake and reducing the hypercalciuria. The concentration of plasma Mg fell significantly ($P < 0.01$) from 1.2±0.02 to 0.79±0.10 meq/liter by the 1st day of the study and remained low throughout.

Mg balance became negative during the 1st day of phosphate depletion and remained so during the entire study. This occurred despite a significant increment in the fraction of ingested Mg absorbed which became evident by the 3rd wk of phosphate depletion. Mg content of muscle, kidney, and liver were not affected but bone Mg was reduced significantly. The change in bone Mg was not due to an overall reduction in bone mineral content because bone calcium content was not affected. Supplementation of large amounts of Mg (800–1,000 μeq/day) in the drinking water produced a normalization of serum Mg but did not bring about restoration of bone Mg despite a positive Mg balance. The disturbances in Mg metabolism were independent of the age or weight of the animals.

Our results indicate that phosphate depletion is associated with (*a*) magnesuria due to a decrease in the net renal tubular reabsorption of Mg with the main source of the urinary losses being bone Mg; (*b*) hypomagnesemia secondary to the renal leak of Mg; (*c*) negative Mg balance; and (*d*) increase in the intestinal fractional absorption of Mg. The latter was not adequate to compensate for the urinary losses of Mg.

INTRODUCTION

Phosphate depletion in rats is associated with hypophosphatemia, hypophosphaturia, hypercalcemia, and hypercalciuria (1–6). Because renal tubular transport of calcium may share a common reabsorptive mechanism or pathway with magnesium (7–9), one might expect magnesuria with phosphate depletion. Data on renal handling of magnesium and its homeostasis during phosphate depletion are limited. Coburn and Massry (10) found that modest magnesuria without consistent changes in plasma magnesium may occur during phosphate depletion in adult dogs. Cuisinier-Gleizes et al. (6), reported a fall in the serum concentration of magnesium and an increase in the urinary magnesium excretion in phosphate-depleted growing rats. The source of the urinary magnesium losses was not identified in their studies. Finally, data on intestinal absorption of magnesium during phosphate depletion are not available.

The present study was undertaken to evaluate the effects of phosphate depletion on magnesium homeostasis with special emphasis on the renal handling, gastrointestinal absorption, and tissue content of magnesium.

METHODS

In preliminary studies in our laboratory we found that rats fed a low phosphate diet do not ingest adequate amounts of food and therefore do not gain weight as animals receiving a normal diet (Fig. 1). Because this phenomenon might affect various physiological functions, the proper control group would be

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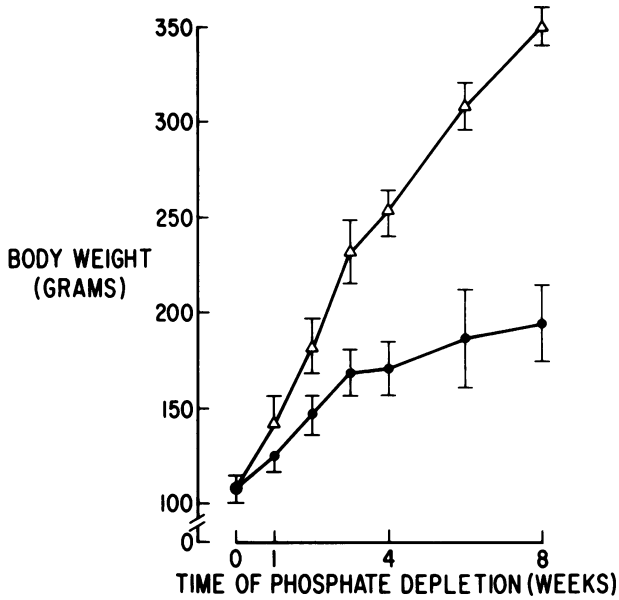

FIGURE 1 The effect of low dietary phosphate on body weight. Closed circles represent data from rats ingesting low phosphate diet and open triangles denote data from rats receiving control diet. Brackets indicate 1 SE.

animals receiving the control diet in an amount adjusted to maintain their weight equal to the phosphate-depleted group.

Male Sprague-Dawley rats 3-wk old were housed in individual metabolic cages for balance studies. After a control period of 5 days, the rats were allocated randomly and subdivided into two groups. The first received a low phosphorus diet (0.03%) and will be referred to as phosphate-depleted (PD)[1] rats. The second group ingested a control diet containing 0.44% phosphorus and were pair weighed to the PD group as described above; these animals will be referred to as pair-weighed (PW) rats. The dietary content of sodium (0.4%), calcium (0.41%), and magnesium (0.03%) were identical in the control and low phosphate diets. All animals had free access to deionized water.

Food intake, urinary and fecal excretions, and weight were measured daily for the first 14 days and then at the last 2 days of the 3rd, 4th, 6th, and 8th wk of PD. Brilliant blue was used as a stool marker. Blood was obtained in heparinized tubes during the control period and on days 1, 4, 7, 14, 21, 28, 42, and 56 of PD. Some of the animals were sacrificed after 3 days and at the end of the 2nd, and 6th wk of PD for measurement of magnesium content in the kidney, liver, skeletal muscle, and bone.

All fecal excretions of each balance period was ashed at 650°C for 24 h in a muffle furnace and then extracted with 0.75 N nitric acid for the measurements of magnesium. Samples of soft tissues were first weighed, then dried at 105°C for 48 h, defatted with ether, redried and weighed. The fat-free dry samples were ashed at 650°C for 24 h in a muffle furnace. The ash was extracted in 0.75 N nitric acid, agitated for 24 h and filtered for subsequent chemical analysis. Tibiae were removed and completely cleaned of soft tissues; and shafts of the tibiae were split longitudinally and the bone marrow removed. Samples of the bone were treated like soft tissues as described above.

To evaluate the possibility that changes in magnesium homeostasis during PD may be related to the age of the animals, studies were carried out in three additional groups of rats that were 6, 8, and 12-wk old.

In another group, nine rats fed a low phosphorus diet had magnesium chloride supplemented for 6 wk in drinking water that contained 0.5% $MgCl_2$. Balance studies were performed in six PD rats and six PW rats receiving $MgCl_2$ supplementation during the 1st wk of the study.

To study the effect of low dietary calcium on the magnesuria, 10 rats 8-wk old were fed a low phosphate diet in which the calcium content was reduced to 0.01%.

To examine the effect of low dietary phosphate on glomerular filtration rate, inulin clearance was measured with [^{3}H]inulin (New England Nuclear, Boston, Mass.) in 11 normal rats, in 12 rats after 2 wk of PD, and in five animals after 8 wk of PD. The measurements were made in awake rats restrained in plastic cages. Radioactive inulin in 0.45% saline was infused in the jugular vein at a rate of 0.05–0.07 ml/min delivering 0.25 μCi/min. After an equilibration period of 60–90 min, urine collections were obtained for three periods of 15–30 min each; blood was obtained from tail vein at the midpoint of each clearance period. The concentration of [^{3}H]-inulin in blood and urine was determined with Beckman liquid scintillation counter, model LS-230 (Beckman Instruments, Inc., Fullerton, Calif.).

Plasma inorganic phosphorus was determined by the micromethod of Chen et al. (11). Plasma, urine, fecal and tissue magnesium, and plasma calcium were measured with the Perkin Elmer atomic absorption spectrophotometer. model 503 (Perkin Elmer Corp., Norwalk, Conn.). Plasma and urine sodium were measured by IL flame photometer (Instrumentation Laboratory, Inc., Lexington, Mass.) whereas plasma and urinary creatinine were determined using a Technicon autoanalyzer (Technicon Instruments Corp., Tarrytown, N. Y.). The statistical significance of the data was assessed by the Student's t test.

RESULTS

After 2 wk of PD, the hair of many of the animals became coarse and patchy areas of hair loss appeared; the exposed skin was erythematous. With prolonged PD, the rats appeared weak and sluggish.

The effects of PD on plasma concentrations of phosphorus and magnesium in rats 3-wk old are shown in Fig. 2. Plasma phosphorus fell significantly ($P < 0.01$) from 10.1±0.27 (SE) to 5.0±0.54 mg/100 within 1 day of feeding the rats a low phosphate diet. This was followed by a continuous and gradual fall to the lowest level of 1.2±0.21 mg/100 ml at the end of the 8th wk of PD. The PW rats maintained their plasma phosphorus within the normal range for the first 2 wk, but the level of phosphorus fell slightly but significantly to 7.1±0.24 mg/100 ml by the end of the 8th wk. The concentration of plasma magnesium fell significantly ($P < 0.01$) from 1.2±.02 to 0.79±0.10 meq/liter during the 1st day of PD and reached its lowest level of 0.48±0.01 meq/liter by the end of the 3rd wk. The plasma magnesium levels in the PW rats did not change. The concentration of serum calcium was 10.2±0.11

[1] *Abbreviations used in this paper*: PD, phosphate depletion(ed); PTH, parathyroid hormone; PW, pair-weighed rats.

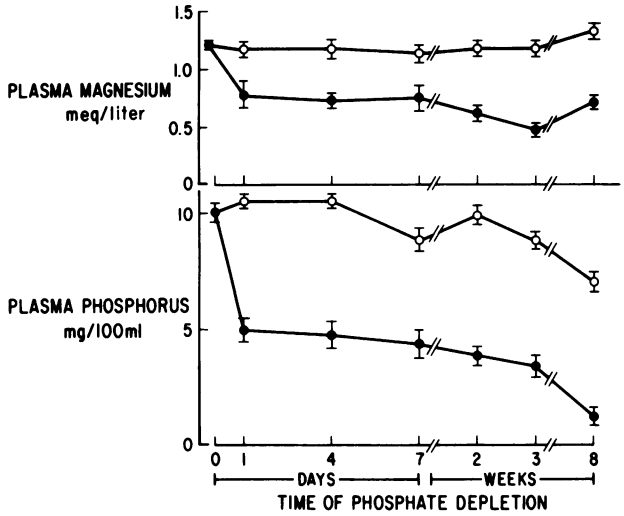

FIGURE 2 Changes in the concentration of plasma magnesium and phosphorus in PD rats (●) and pair-fed rats (○). Brackets denote 1 SE.

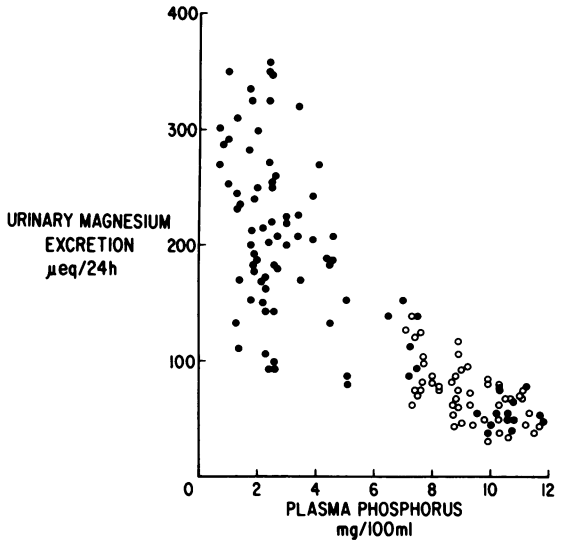

FIGURE 4 The relationship between the concentration of phosphorus in plasma and urinary excretion of magnesium. Closed symbols denote data from rats ingesting a low dietary phosphate and open symbols represent data from pair-fed animals.

mg/100 ml before PD and 12.4±0.44, 12.4±0.20, 12.0±0.36, 9.9±1.70, 10.4±0.21 mg/100 ml at 1, 2, 4, 6, and 8 wk of PD.

A significant ($P < 0.01$) increment in urinary magnesium excretion from 46±2.7 to 126±24 μeq/24 h was noted during the 1st day of PD. Urinary magnesium continued to increase and reached its peak of 300±24 μeq/24 h during the 3rd day and remained high fluctuating between 150–300 μeq/24 h thereafter (Fig. 3). The magnitude of the magnesuria was related to the degree of hypophosphatemia (Fig. 4); the correlation coefficient for this relationship is 0.74 with $P < 0.01$. The PW rats did not display a substantial change in urinary magnesium. The PD rats also displayed marked hypercalciuria; urinary calcium increased from a control value of 0.40±0.09 mg/24 h to 23.3±3.2 mg/24 h ($P < 0.01$) on the 3rd day of PD. This is in contrast to PW rats that had no significant change in urinary calcium excretion (from control value of 0.41±0.06 to 0.34±0.06 mg/24 h).

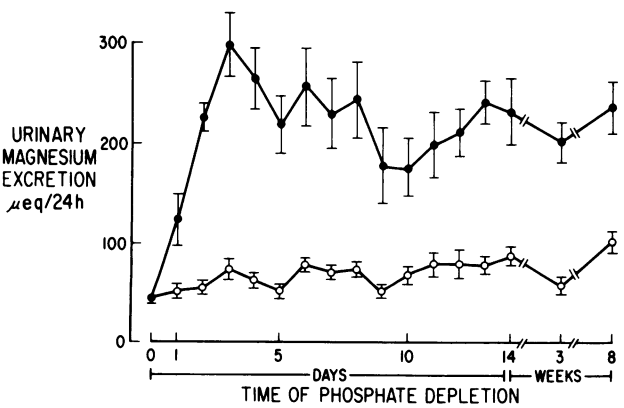

FIGURE 3 The changes in urinary excretion of magnesium in rats with PD (●) and in pair-fed rats (○). Brackets denote 1 SE.

The concentration of serum creatinine did not change during PD; it was 0.42±0.02 mg/100 ml before PD and 0.53±0.04, 0.50±0.05, 0.43±0.05, and 0.47±0.03 mg/100 ml at 1, 2, 4, and 8 wk of PD respectively. The 24 h excretion of creatinine was 2.1±0.16 mg/100 g body wt per 24 h before PD and 2.8±0.38, 2.9±0.21, 2.7±0.16, and 3.2±0.14 at 1, 2, 4, and 8 wk of PD indicating the adequacy of urinary collection. Measurements of endogenous creatinine clearance several times throughout the study were not different from values in PW rats. Furthermore, measurements of glomerular filtration rate with radioactive inulin revealed no significant effect of PD. The glomerular filtration rate was 1.27±0.01 ml/min per 100 g body wt in normal rats, 1.19±0.01 ml/min per 100 g body wt after 2 wk of PD, and 1.00±0.15 ml/min per 100 g body wt after 8 wk of PD. The blood levels of sodium did not change and sodium excretion was not affected significantly by low dietary phosphorus. It was 1,388±163 μeq/24 h before PD and 1,330±218, 1,550±154, and 1,598±274 μeq/24 h at the end of the 1st, 3rd, and 8th wk of PD, respectively.

The data on the balance of magnesium during low phosphorus intake are shown in Fig. 5. Despite the significant magnesiuria, fecal magnesium did not change significantly during the first 2 wk of low dietary phosphorus, and the fraction of ingested magnesium absorbed ranged between 0.48±0.05 and 0.61±0.04

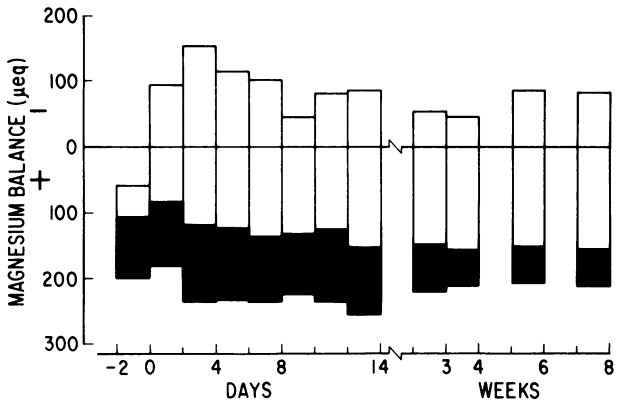

FIGURE 5 Magnesium balance in rats fed a low phosphate diet. Open bars indicate urinary excretion of magnesium and solid bars represent fecal magnesium.

during this period. These values are not significantly different from the control values of 0.55±0.03. However, the fraction of ingested magnesium absorbed increased significantly ($P < 0.01$) to values of 0.69±0.06 and 0.74±0.03 during the 3rd–8th wk of the study. The balance of magnesium became negative during the 1st day of low dietary phosphorus and remained so throughout the entire study.

The results on magnesium content in various tissues and data on bone calcium are given in Table 1. There were no significant differences between the magnesium content of the muscle, kidney, and liver of PD and PW rats. In contrast, the magnesium content in bone displayed a modest and significant ($P < 0.01$) decrease within 3 days of feeding with low dietary phosphate. The difference between the magnesium content of bone in PD and PW rats becamse greater at 14 and 42 days of the study ($P < 0.01$). The calcium content of bone in PD rats was not different from that of PW rats. The calcium to magnesium ratio in bone of PD rats was, therefore, significantly higher than that in PW rats.

The PD rats receiving $MgCl_2$ in their drinking water maintained blood levels of magnesium (1.25±0.04 meq/liter and did not display hypomagnesemia despite decrements in the levels of serum phosphorus similar to those noted in PD rats without $MgCl_2$ supplementation. Despite a four- to fivefold increment in magnesium intake by these rats, the content of magnesium in bone remained low and was not different from that observed in PD rats without $MgCl_2$ supplementation (Table I). The balance data during the 1st wk of the study in six PD rats and six PW rats receiving $MgCl_2$ supplementation are given in Table II. Although the PD rats had a positive magnesium balance, the magnitude of the positive balance was significantly ($P < 0.01$) lower than in PW rats receiving the same amount of magnesium supplementation.

The effects of low phosphorus intake on the levels of serum phosphorus and magnesium and on urinary excretion of magnesium in older rats are presented in Table III. As in the younger rats, PD produced a significant fall in the concentrations of serum phosphorus and magnesium ($P < 0.01$) and a significant increment in urinary magnesium ($P < 0.01$) in rats 6, 8, and 12-wk old. In these rats, the urinary excretion of magnesium before PD was greater than in the younger rats. This is at least partly due to greater amounts of food ingested by the older rats. As in the case of the younger rats, the older animals had marked hypercalciuria. Urinary calcium increased by the 3rd day of PD to 18.4±2.2, 10.9±2.2, and 15.2±3.5 in rats 6, 8, and 12-wk old respectively.

The effect of low dietary phosphate and calcium on

TABLE I

Effect of a Low Dietary Phosphorus on Tissue Content of Magnesium and on Bone Magnesium and Calcium

Group	Magnesium				Bone calcium	Calcium/Magnesium
	Muscle	Liver	Kidney	Bone		
	meq/100 g fat-free dry wt				*meq/100 g fat-free dry wt*	
1 3 days						
PD	10.6±0.52	7.9±0.23	8.6±0.32	29.4±2.29*	1,334±25.2	49.1±4.06*
PW	10.9±0.36	7.1±0.33	8.8±0.52	38.7±1.45	1,385±21.9	35.9±1.44
2 14 days						
PD	8.7±0.03	6.5±0.12	8.3±0.13	23.6±0.48*	1,138±35.2	48.1±0.97*
PW	9.8±0.07	6.7±0.11	8.7±0.21	37.5±0.82	1,154±11.6	31.0±0.45
3 42 days						
PD	11.7±0.38	7.0±0.25	9.1±0.29	23.9±0.91*	1,183±31.2	49.5±1.19*
PW	11.7±0.41	6.7±0.23	9.4±0.22	41.6±1.30	1,236±30.5	29.8±0.70
PD + $MgCl_2$	12.2±0.24	6.8±0.26	9.2±0.33	23.0±1.09*		

* Indicates values significantly different ($P < 0.01$) from PW rats.

TABLE II
Balance Data in Six PD rats and Six PW Rats Receiving Magnesium Supplementation during the 1st Wk of the Study

		Days		
		2 and 3	4 and 5	6 and 7
Magnesium intake, *μeq/24 h*	PD	1,164±57.0	1,161±79.1	1,124±95.0
	PW	1,175±81.2	1,180±69.8	1,164±58.0
Fecal magnesium, *μeq/24 h*	PD	411±47.5	458±64.7	451±68.5
	PW	426±51.0	463±27.0	449±67.8
Urinary magnesium, *μeq/24 h*	PD	493±36.1*	471±38.2*	485±46.1*
	PW	350±20.9	330±27.0	340±32.1
Magnesium balance, *μeq/24 h*	PD	+260±36.5*	+232±68.7*	+188±88.1*
	PW	+399±35.3	+385±37.3	+375±41.0

Data are presented as Mean±SEM.
* Indicate value is significantly different ($P < 0.01$) from PW rats.

urinary magnesium and calcium are given in Table IV. In these animals, urinary magnesium also increased to more than 300 meq/24 h but the hypercalciuria was markedly and significantly (<0.01) less than in PD rats receiving higher calcium intake. Calcium excretion increased from 0.06±0.03 to 1.17±0.18 mg/24 h.

DISCUSSION

The results of the present study demonstrate that PD in the rat is associated with significant increments in the urinary excretory rates of magnesium, significant decrements in the concentration of magnesium in the blood, and negative magnesium balance. Other investigators have reported variable degrees of magnesuria during PD in rats (6) dogs (10), and man (12).

An increase in urinary magnesium may follow enhanced intestinal absorption of this ion, an increase in its filtered load, augmented release of magnesium from bone and (or) soft tissues, a decrease in its renal tubular reabsorption, or secretion of magnesium by the nephron. Our data does not support the first two possibilities. The increase in urinary magnesium occurred before any evident change in its intestinal absorption and at a time when the blood levels of magnesium fell, and consequently filtered loads of magnesium were lower than control levels.

Magnesium content of bone was decreased by the end of 3 days of feeding the rats a low phosphate diet and remained low throughout the study. This was not due to an overall reduction in mineral content of bone, because changes in calcium content of bone were not detected during PD. At least two possibilities could account for the fall in bone magnesium. First, PD is associated with the formation of magnesium-poor bone in these growing rats; and second, PD may enhance magnesium release from bone. Our data suggest that both of these mechanisms may be operative. The findings that rats with PD developed negative magnesium balance despite similar dietary intake of magnesium and in the face of no decrease or even an increase in the fraction of ingested magnesium absorbed favors loss of magnesium from body stores. Because only bone displayed a decrease in its magnesium content, it is reasonable to assume that PD is associated with an augmented release of magnesium from the skeleton. However, the observation that bone content of magnesium remained low despite positive magnesium balance in PD rats receiving magnesium supplementation is consistent with the formation of magnesium-poor bone. The inability to increase bone magnesium to normal despite positive magnesium balance is not surprising because the net balance is still negative when compared to PW rats receiving similar amounts of magnesium supplementation.

The magnesium loss from bone may be the primary event in the genesis of the magnesuria but it may also be secondary to renal magnesium leak. It is well documented that a normally functioning kidney has a tremendous magnesium conserving ability (13–15), and in the presence of hypomagnesemia not due to primary renal loss, magnesium virtually disappears from the urine (13–15). The demonstration in the present study that marked magnesuria persisted despite the hypomagnesemia favors the postulate that PD induces renal magnesium wasting with the bone being the source of the urinary magnesium losses. It is of interest that the amount of magnesium that is required to prevent the fall in its blood levels is very small (15–20 μeq) compared to the increments in urinary magnesium. This quantitative disparity and the observation that levels of blood magnesium were maintained at normal values only after the supplementation of very large quantities of magnesium (800–1,000 μeq/day) provides further support for a primary renal leak of magnesium.

Other factors beside urinary magnesium losses may contribute to the hypomagnesemia in our PD growing rats. It is interesting that PD in humans is associated with magnesiuria but with only minor changes in the levels of serum magnesium (12), and in our PD adult rats, the fall in the concentration of serum magnesium was less than in the younger rats despite similar or even greater magnesuria. It is possible that the need for magnesium by newly formed bone in the PD growing rats, which are in negative magnesium balance, contributes to the magnitude of the hypomagnesemia.

TABLE III

Effect of Low Dietary Phosphorus on the Concentration of Serum Inorganic Phosphorus and Magnesium and Urinary Excretion of Magnesium in Rats 6-, 8-, and 12-Wk Old

			Days after low phosphate diet													
		Control	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Group 1	Weight, *g*	183±8							208±6							228±9
n = 5	Age, *wk*	6							7							8
	Serum P, *mg/100 ml*	9.5±0.28	4.2±0.50*		4.1±0.93*		5.1±2.8*		5.2±0.70*			4.6±0.64*				4.7±0.53*
	Serum Mg, *meq/liter*	1.54±0.07	1.19±0.05*		0.89±0.16*		0.69±0.03*		0.89±0.05*			0.94±0.05*				0.96±0.07*
	Urinary Mg, *μeq/24 h*	122±15	170±23	289±28*	328±28*	314±15*	254±20*	214±35*	237±18*	207±21*	230±20*	237±31*	180±16*	201±23*	237±18*	214±23*
Group 2	Weight, *g*	271±7							282±6							298±8
n = 5	Age, *wk*	8							9							10
	Serum P, *mg/100 ml*	9.5±0.32	3.4±0.25*		3.3±0.37*		4.7±0.50*		4.4±0.29*			3.6±0.32*				5.8±0.45*
	Serum Mg, *meq/liter*	1.51±0.04	1.30±0.03*		1.19±0.07*		1.16±0.03*		1.10±0.06*			1.03±0.03*				1.07±0.06*
	Urinary Mg, *μeq/24 h*	124±14	144±21	280±38*	344±39*	288±30*	206±31*	213±23*	253±32*	209±17*	224±31*	217±26*	199±20*	192±26*	222±21*	215±25*
Group 3	Weight, *g*	311±15							342±11							358±10
n = 5	Age, *wk*	12							13							14
	Serum P, *mg/100 ml*	9.5±0.13	3.9±0.55*		3.2±0.37*		4.6±0.30*		3.8±0.30*			3.0±0.21*				5.1±0.38*
	Serum Mg, *meq/liter*	1.41±0.04	1.29±0.10		1.19±0.05*		1.12±0.08*		1.05±0.07*			1.10±0.07*				1.12±0.07*
	Urinary Mg, *μeq/24 h*	126±18	144±39	348±39*	431±60*	351±44*	343±36*	304±51*	321±26*	320±28*	328±46*	349±30*	272±33*	261±26*	319±48*	319±53*

Abbreviations: P, phosphorus; and Mg, magnesium.

* Represent significantly different values from control with $P < 0.01$.

TABLE IV

Effect of Low Dietary Phosphorus and Calcium on the Concentration of Serum Inorganic Phosphorus, Magnesium and Calcium and Urinary Excretion of Magnesium and Calcium

		Days after low phosphate and calcium diet						
	Control	1	2	3	4	5	6	7
Weight, *g*	266±5							275±5
Age, *wk*	8							9
Serum P, *mg/100 ml*	9.2±0.24		6.4±0.27		6.4±0.29			5.1±0.23
Serum Mg, *meq/liter*	1.70±0.05		1.44±0.05		1.2±0.03			1.2±0.04
Urinary Mg, *μeq/24 h*	200±10	210±21	275±22	300±26	320±19	320±18	317±19	333±18
Serum Ca, *mg/100 ml*	10.3±0.08		10.0±0.12		10.1±0.09			10.2±0.14
Urinary Ca, *mg/24 h*	0.60±0.03	0.65±0.10	0.93±0.14	1.17±0.18	1.36±0.25	1.38±0.26	1.3±0.20	2.5±0.62

Data are presented as mean±SE.

Abbreviations: P, phosphorus; Mg, magnesium; Ca, calcium.

Our data indicate that a decrease in the net tubular reabsorption of magnesium occurs during PD because the magnesiuria persisted despite a decrease in filtered loads of magnesium. The mechanisms responsible for this phenomena are not clear. Several possibilities should be considered. First, this defect is obviously not related to the age or the weight of the rats because it occurred in animals of different ages and weights. Second, a reduction in the tubular reabsorption of magnesium usually occurs with conditions causing natriuresis (15–18). In our animals, magnesiuria developed in the absence of changes in urinary sodium excretion.

Third, magnesiuria occurs in animals (19, 20), or humans (21) under the influence of chronic mineralocorticoid excess. It is possible that PD induces the release of steroids with mineralocorticoid properties, although this possibility seems remote. Animal studies have shown that with initiation of mineralcorticoid administration, there is a period of sodium retention without magnesiuria, but urinary magnesium excretion increases as the animals escape the sodium retaining effect of the hormone (20). In our study, magnesuria occurred during the 1st day of PD and there was no evidence of sodium retention.

Fourth, PD has been reported to cause hypofunction of the parathyoid glands (12, 22) and because parathyroid hormone (PTH) enhances magnesium reabsorption (23, 24), partial or complete lack of PTH could cause modest magnesuria. However, the data of Cuisinier-Gleizes et al. (7) argues against this possibility. They found that magnesuria occurred in thyroparathyroidectomized PD rats. Also, available data indicate a resistance to the phosphaturic action of PTH in PD rats (25). Theoretically, a resistance to the action of PTH on renal handling of magnesium may develop during PD and as such contribute to the magnesuria.

Fifth, mild elevation in the blood levels of calcium develop during PD (1, 6, 10, 26), and this may be, at least, partly responsible for the magnesuria because hypercalcemia decreases the renal tubular reabsorption of magnesium (9). Indeed, the concentration of blood calcium in our rats increased by 1.0–2.0 mg/100 ml during the first 4 wks of PD. However, the blood levels of calcium returned to normal between the 5th and 8th wk of PD but the magnesuria persisted. These observations clearly indicate the renal magnesium wasting during PD could not be entirely explained by the changes in the concentration of calcium in the blood. Also, hypercalciuria of PD may play a role in the genesis of the magnesiuria. However, this seems unlikely because marked magnesiuria persisted when the hypercalciuria was markedly blunted in rats fed a low phosphate and calcium diet.

Finally, preliminary data by Ben-Isaac et al. (27) showed that the blood of PD rabbits contains a humoral factor which suppresses the tubular reabsorption of calcium. It is well documented that the renal handling of calcium and magnesium is closely related (7–9), and it is reasonable to assume that such a humoral factor may also reduce the tubular transport of magnesium.

A decrease in the net tubular reabsorption of magnesium during PD is not surprising because others have reported tubular reabsorptive defects of other substances such as calcium (10), bicarbonate (28), glucose (29), and sodium (30).

One should also consider the possibility that PD may

be associated with renal tubular secretion of magnesium. The evidence for the existence of magnesium secretion by the renal tubule is conflicting. Although Averill and Heaton (31) demonstrated magnesium secretion in the rat during magnesium loading, Alfredson and Walser (32) failed to confirm this observation. Recent micropuncture data obtained in magnesium-loaded rats suggest that magnesium may be secreted by the descending limb of the loop of Henle (33). In the dog, Massry et al. (24) were unable to show tubular secretion of magnesium although others found that urinary magnesium may reach values that are 10–20% greater than filtered magnesium during the concomitant administration of magnesium salts, saline, and furosemide (34). It appears that if magnesium secretion by the nephron exists, it plays a minor role in the renal handling of magnesium.

It is evident that PD can induce marked alteration in magnesium homeostasis. Our data permit the formulation of a certain sequence of events in the relationship between body stores of phosphate and magnesium metabolism. It appears that PD induces, by as yet, undertermined mechanism(s) a decrease in the tubular reabsorption of magnesium and results in magnesuria. The enhanced urinary losses of this ion are followed by hypomagnesemia and negative magnesium balance with bone being the main organ affected. An adaptive augmentation in the fractional intestinal absorption of magnesium occurred only after a prolonged period of PD and when the cumulative negative balance of magnesium was marked.

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