JCI The Journal of Clinical Investigation

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J Clin Invest. 1966;45(5):672-677. https://doi.org/10.1172/JCI105382.

Research Article

Journal of Clinical Investigation
Vol. 45, No. 5, 1966

The Control of Phosphate Excretion in Uremia *

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The patterns of phosphate excretion in man with advancing chronic renal disease are well established. Although phosphate clearance decreases with time, it falls proportionately less than glomerular filtration rate, and the ratio of phosphate clearance to GFR increases as the disease advances (1). Thus the average rate of phosphate excretion per residual nephron increases as the nephron population diminishes, and the onset of hyperphosphatemia thereby is delayed. The explanation for this sequence is of considerable theoretical interest. The major possibilities are two: *1*) The change could reflect the operation of a control system geared either to maintain external phosphate balance or to maintain plasma phosphate concentrations constant; *2*) the relative phosphaturia per nephron could be a consequence of uremia or of the abnormalities in residual nephrons or both. These studies represent an attempt to distinguish between these two interpretations using the dog with intrinsic renal disease as the experimental model. The experiments also were designed to delineate the general characteristics of a control system, should one exist.

Methods

A total of 80 experiments was performed on 30 female mongrel dogs ranging in weight from 12 to 20 kg. The animals were fed standard dog chow, and supplementary horsemeat was given to assure a daily phosphate intake of at least 0.5 g. A preliminary bladder-splitting operation was performed to permit the quantitative collection of urine from the individual kidneys without recourse to ureteral catheterization (2). Thereafter, unilateral pyelonephritis was induced by a technique described previously (3). In five dogs, the diseased kidney was studied in the presence of the control kidney, and the functions of the two organs were compared. These experiments were similar in design to those described in a previous publication (4) and were performed to verify the previous results in the present animals. In 27 dogs, the control kidneys were removed to permit investigation of the diseased kidneys under environmental conditions varying from moderate azotemia to severe uremia.

Three groups of animals were subjected to special experimental maneuvers. In six dogs, GFR was reduced during clearance measurements either by constriction of the renal artery of the diseased kidney or by graded phlebotomy. Arterial constriction was accomplished with an arterial clamp that was placed about the renal artery just before initiation of clearance measurements. In six dogs, phosphate levels in the plasma were lowered by administration of aluminum carbonate gel by stomach tube for 3 days. A total of 150 ml per day was given in divided doses. Experiments were performed before and after this phosphate-depleting procedure. Finally, in eight dogs, thyroparathyroidectomy was performed to observe the effects of eliminating parathyroid hormone activity on phosphate excretion. Removal of parathyroid tissue was judged to be complete only if the animals became hypocalcemic and developed clinical manifestations of tetany. Seven of the eight dogs satisfied these criteria.

With the exception of the renal arterial constriction experiments, all clearance measurements were performed with the animals in the unanesthetized state. In most experiments, GFR was measured by the exogenous creatinine clearance. In the renal arterial constriction experiments inulin clearance was used to measure GFR, and in the prolonged phlebotomy experiments, GFR was estimated by endogenous creatinine clearance. Creatinine was measured by the method of Bonsnes and Taussky (5), inulin by the method of Roe, Epstein, and Goldstein (6), and phosphate by the method of Gomori (7). Plasma urea nitrogen levels were determined manometrically according to the method of Van Slyke and Kugel (8), and serum calcium concentrations were estimated by flame photometry. Additional details of the experimental techniques have been presented previously (3).

* Submitted for publication December 13, 1965; accepted January 12, 1966.

Supported in part by research grants AM-02667 and AM-09976 from the U. S. Public Health Service and by U. S. Public Health Service graduate training grant T1 AM-5248.

Presented at the National Meeting of the American Federation for Clinical Research, Atlantic City, N. J. An abstract has been published (Clin. Res. 1965, 13, 315).

† Career Research Award, U. S. Public Health Service.

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Results

It is conventional to describe phosphate excretion in terms of the apparent tubular reabsorption of phosphate or TRP.[1] Although this term is a valid expression for the percentage of filtered phosphate reabsorbed only if there is no tubular secretion of phosphate, the interpretations of the present experiments would not be modified substantively if secretion of phosphate occurred.

In Table I, data are shown for the five animals that were studied with a control kidney *in situ*. Values for the diseased kidneys are compared with those for the contralateral control organs that were free of disease. In relation to the control kidneys, GFR for the diseased organs was reduced by from 27 to 93%. TRP averaged 92.8% for the diseased kidneys and 91.3% for the control organs. These values are not significantly different ($p > 0.50$). The lowest value for TRP in any kidney was 85%, and values for eight of the ten kidneys were 89% or greater.

TABLE I

*Comparison of phosphate excretion in diseased and contralateral control kidneys**

Dog	C_{Cr} Exp.	C_{Cr} Cont.	P_{PO_4}	TRP Exp.	TRP Cont.
	ml/min		*mg/100 ml*	%	
1	8.8	51.9	3.2	94.8	89.6
2	16.3	40.1	4.0	95.8	97.1
3	27.7	43.8	4.3	94.9	92.7
4	4.6	66.7	4.2	93.3	90.0
5	24.0	64.2	5.0	85.0	87.3
Mean value	16.3	53.3	4.1	92.8	91.3
SD	± 9.8	±11.9	±0.2	± 4.4	± 3.8

* All results are the average of three or more clearance periods in this and succeeding Tables. C_{Cr} = creatinine clearance; P_{PO_4} = plasma phosphate concentration; TRP = tubular reabsorption of phosphate; exp. = experimental (i.e., diseased) kidney; cont. = contralateral control kidney.

Table II summarizes the results from the 27 dogs in which experiments were performed after the control kidneys had been removed and the diseased kidneys provided the only source of renal function. GFR averaged 14.5 ml per minute with a range of 2.7 to 30.8 ml per minute. The plasma urea nitrogen concentrations ranged from 23 to 150 mg per 100 ml and averaged 63.6 mg per 100 ml for the group. The mean value for plasma phosphate concentrations was 6.5 mg per 100 ml with a range of 4.0 to 13.9. In contrast to the animals in which a normal control kidney contributed to renal function, TRP was markedly depressed, averaging 48.9% for the 27 dogs. The range of TRP values was from 27.7 to 79.0%; thus in all 27 dogs, TRP values were lower than

TABLE II

*Summary of studies performed on 27 dogs with control kidneys removed and diseased kidneys providing the only source of renal function**

	GFR	PUN	P_{PO_4}	TRP
	ml/min	*mg/100 ml*	*mg/100 ml*	%
Mean value	14.5	63.6	6.5	48.9
SD	± 7.7	±12.3	±2.2	±14.3

* GFR = glomerular filtration rate; PUN = plasma urea nitrogen. Other terms are defined in the footnote to Table I.

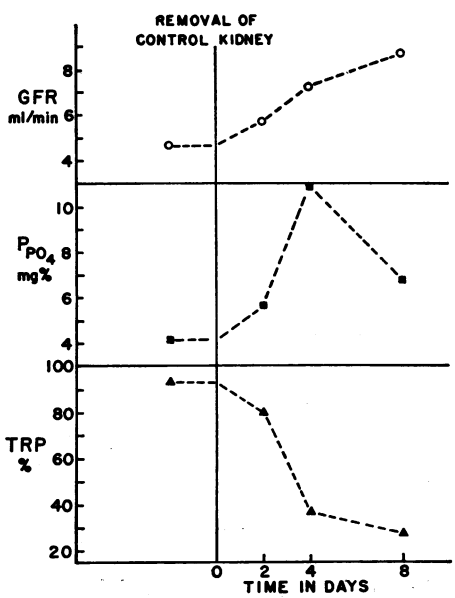

FIG. 1. SEQUENTIAL CHANGES EVOKED BY REMOVAL OF THE CONTROL KIDNEY IN A DOG WITH SEVERE UNILATERAL PYELONEPHRITIS. The initial studies were performed before removal of the control kidney. Values for the control kidney were as follows: glomerular filtration rate (GFR) = 66.7 ml per minute; tubular reabsorption of phosphate (TRP) = 90%. P_{PO_4} = plasma phosphate concentration.

[1] $TRP = (1 - C_{PO_4}/GFR) \times 100$, where C_{PO_4} = phosphate clearance.

TABLE III

*The effects of decreasing GFR on C_{PO_4} and TRP of the diseased kidney**

Dog	Clearance period	C_{Cr}	C_{In}	P_{PO_4}	C_{PO_4}	TRP†
		ml/min	*ml/min*	*mg/100 ml*	*ml/min*	%
Constriction of renal artery						
A	1–3 (control)	16.9	18.7	5.4	7.1	62.0
	4	8.4	8.6	5.1	2.7	68.6
	5	13.2	13.3	5.0	3.6	72.9
	6	15.5	16.2	5.1	4.2	74.1
	7	6.9	6.9	5.6	2.2	68.1
	8	7.1	7.4	5.8	2.4	67.6
	9	7.8	8.1	5.6	2.8	65.4
B	1–3 (control)	22.8	23.0	5.63	12.9	44.0
	4	12.3	12.4	5.60	7.9	36.3
	5	12.4	14.4	5.60	8.3	42.4
	6	12.5	15.4	5.60	8.2	46.8
C	1–3 (control)	14.3	11.6	5.4	6.6	43.0
	4	13.7	11.5	4.3	4.79	58.0
	5	10.5	10.1	4.9	2.66	74.0
	6	9.7	9.3	5.5	3.50	62.4
	7	8.7	7.6	6.1	3.70	51.0
Phlebotomy						
D	1–3 (control)	6.28		12.0	4.26	33.0
	4	5.31		11.4	3.76	29.2
	5	5.03		11.8	3.44	31.6
	6	4.60		11.8	3.02	34.0
	7	3.20		11.3	2.16	32.5
	8	2.75		11.3	1.80	34.6
	9	1.78		12.8	1.01	44.3
	10	1.45		13.0	0.82	43.0
	11	0.64		13.3	0.40	37.5
E	1–3 (control)	21.6		5.6	7.92	63.0
	4	19.5		5.3	7.75	60.3
	5	16.1		5.2	5.02	68.8
	6	15.8		5.3	5.01	68.3
	7	15.1		5.0	4.59	69.6
	8	10.7		4.3	2.90	72.9
F	1–3 (control)	1.80		15.2	1.51	16.0
	4	1.68		16.1	1.35	19.7
	5	1.36		15.9	1.11	19.4
	6	1.32		16.8	1.06	19.7
	7	1.19		16.9	0.92	22.7
	8	0.86		16.8	0.73	15.0

* Three control clearance periods were obtained before either renal arterial constriction or phlebotomy was initiated. In the phlebotomy experiments no infusions were employed, and GFR was approximated with endogenous clearance. In the renal arterial constriction experiments inulin clearance was used to measure GFR. Endogenous creatinine values were also determined in these experiments, and the values are included for comparison with the inulin clearances. The priming and sustaining infusions of inulin were calculated to achieve plasma inulin concentrations of approximately 25 mg per 100 ml. The clearance periods ranged from 20 to 60 minutes in duration. C_{In} = inulin clearance; C_{PO_4} = phosphate clearance; other terms are defined in Table I.
† Calculation using C_{In} in the renal arterial constriction experiments.

85%, the minimal value recorded in Table I for the nonuremic animals.

The sequential changes evoked by the removal of the control kidney are depicted graphically in Figure 1 for an animal with severe unilateral pyelonephritis. The initial studies were performed 6 weeks after disease was induced in the experimental kidney, but before removal of the control kidney. The GFR for the diseased kidney was 4.6 ml per minute. After nephrectomy, GFR increased over the 8-day period of study to approximately twice its initial value. The plasma phosphate concentrations increased strikingly from the prenephrectomy value of 4.1 mg per 100 ml to 11 mg per 100 ml; but the peak was reached on the fourth day, and on the eighth day, the value had decreased to 6.7 mg per 100 ml. TRP was 93% in the initial study. Two days after nephrectomy, the value was 80%. Four days after nephrectomy, it was 36%. On the eighth day, the TRP was 29%.

The increase in GFR depicted in Figure 1 is a characteristic occurrence in the diseased kidney of the dog after the contralateral control kidney is removed (3). To evaluate the possibility that hyperfiltration was responsible for the depression of TRP, we assessed the effects of experimental reduction in GFR on phosphate excretion. In three animals GFR was reduced by constricting the renal artery; in another three animals GFR was diminished by graded phlebotomy carried out over periods ranging from 4 to 6 hours. In both groups three control periods were obtained before reducing GFR. The data are presented in Table III. Regardless of the degree of reduction of GFR (the maximal reduction varied from 27 to 90%), TRP was not restored to a normal

TABLE IV

*The effects of decreasing plasma phosphate concentrations on phosphate excretion**

Experiment		P_{PO_4}	P_{Ca}	C_{Cr}	FL	C_{PO_4}	TRP
		mg/100 ml	*mg/100 ml*	*ml/min*	*mg/min*	*ml/min*	%
1	Pre	4.9	9.7	7.7	0.38	4.6	40.3
	Post	2.5	10.2	8.4	0.21	4.0	52.4
2	Pre	7.2	8.6	10.4	0.75	7.9	24.0
	Post	4.5	10.0	13.7	0.62	7.7	43.8
3	Pre	5.9	9.4	11.4	0.67	5.4	52.6
	Post	4.1	11.8	13.7	0.56	2.1	84.7
4	Pre	13.9	9.2	8.3	1.15	6.9	16.9
	Post	5.3	10.0	6.5	0.34	5.3	18.5
5	Pre	4.9	8.7	16.7	0.82	8.5	49.1
	Post	3.9	10.8	14.7	0.57	3.1	78.9
6	Pre	5.0	8.5	20.0	1.00	8.8	56.0
	Post	3.8	10.0	22.7	0.86	6.7	70.5
Mean	Pre	7.0	9.0	12.4	0.80	7.0	39.8
	Post	4.0	10.5	13.3	0.53	4.8	58.1

* Pre and post refer to the studies performed before and after aluminum carbonate gel administration. No Donnan correction was applied in calculating the filtered load of phosphate (FL). P_{Ca} = plasma calcium concentration.

range, and in most animals the increments were modest. The highest value achieved for TRP was 74.1 in dog A. In dog D, although creatinine clearance was reduced slowly over a 6-hour period from 6.3 ml per minute to 0.64 ml per minute, TRP increased only from 33% to a maximal value of 44.3%.

The effects of decreasing the filtered load of phosphate by lowering the serum concentration of phosphate are shown in Table IV. Studies were performed before and immediately after a 3-day period of aluminum carbonate gel administration. The decrease in plasma phosphate concentrations ranged from 1.0 to 8.6 mg per 100 ml, and filtered phosphate decreased by an average of 34%. A reciprocal increase in plasma calcium levels was observed in each of the six animals. In one animal (experiment 3), the TRP increased from 52.6 to 84.7, and in another (experiment 5) the value rose from 49.1 to 78.9. However, in the other four dogs, the increments were small, and for the group the mean value for TRP increased from 39.8% to 58.1%.

Table V presents the data obtained from the seven animals studied before and after thyroparathyroidectomy. TRP averaged 55.1% (range 41 to 78.2%) before parathyroidectomy. The values obtained after the surgical induction of hypoparathyroidism were increased strikingly. In three dogs the values exceeded 90%, and in one of these (dog 7) TRP averaged 98%. The mean value for the seven dogs was 88.9%. After completion of three to four clearance periods in the parathyroidectomized animals, 250 U of a parathyroid hormone preparation [2] was administered intravenously, and three additional 20-minute clearance periods were obtained. Under the influence of exogenous parathyroid hormone, the TRP values decreased markedly in all animals, and the mean value for the group closely approximated the preparathyroidectomy level (i.e., 54.0% vs. 55.1%).

Discussion

When chronic renal disease exists in only one kidney and there is a contralateral kidney present that is free of disease, the total number of nephrons is not greatly diminished. In this setting, values for TRP in the chronically diseased kidney of the dog characteristically exceed 75% and often are in excess of 85% [(4) and Table I]. Moreover, the values for the diseased kidneys are closely comparable to those of the contralateral organs regardless of the severity of the unilaterial lesion. However, when the nephron population was diminished markedly by removing the normal kidney, the TRP in the residual nephrons of the diseased organs decreased strikingly, and the pattern characteristic of uremic man (1) was reproduced in the uremic dog (Table II). This decrease in TRP implies that the average rate of phosphate excretion per nephron increased. If such a change in phosphate excretion is initiated and sustained by a control mechanism, rather than by the fortuitous emergence of a defect in phos-

[2] Parathormone, Eli Lilly, Indianapolis, Ind.

TABLE V

The effects of thyroparathyroidectomy and PTH infusion on PO_4 excretion

Dog	Before thyroparathyroidectomy				After thyroparathyroidectomy						
					Before PTH				After PTH*		
	GFR	P_{PO_4}	P_{Ca}	TRP	GFR	P_{PO_4}	P_{Ca}	TRP	GFR	P_{PO_4}	TRP
	ml/min	*mg/100 ml*	*mg/100 ml*	%	*ml/min*	*mg/100 ml*	*mg/100 ml*	%	*ml/min*	*mg/100 ml*	%
1	7.6	7.5	10.0	51.4	5.0	5.9	7.8	93.0	6.8	5.5	48.7
2	7.7	4.4	9.7	41.0	12.6	3.7	6.4	93.9	11.2	3.5	75.0
3	11.4	5.9	9.4	52.6	12.0	6.1	5.6	89.0	16.1	4.1	58.9
4	16.4	4.9	8.8	49.1	14.4	4.7	6.8	73.8	17.0	4.7	41.2
5	20.5	4.6	9.1	47.3	14.8	5.6	4.4	88.6	19.0	5.0	46.8
6	30.7	4.3	8.7	65.8	41.5	5.4	7.7	85.9	41.6	4.1	47.4
7	30.8	6.2	9.8	78.2	25.6	5.6	7.8	98.0	26.8	4.5	59.7
Mean	17.9	5.4	9.4	55.1	18.0	5.3	6.6	88.9	19.8	4.5	54.0
SD	± 9.9	±1.2	± 0.5	± 12.9	±12.0	±0.8	±1.3	± 7.8	±11.5	±0.2	±10.2

* 250 U of parathyroid hormone (PTH) was administered intravenously in a single injection.

phate reabsorption, three different factors may be considered as possible effector mechanisms.

1) Since removal of the normal kidney in this model is associated with an adaptive increase in GFR in the diseased kidney (3), hyperfiltration could underlie the relative phosphaturia.

2) Plasma phosphate concentrations were elevated in many of the uremic dogs. The attendant increase in the filtered load of phosphate could contribute to the phosphaturia.

3) Secondary hyperparathyroidism, which characteristically occurs in uremia (9–11), could play the dominant role in the altered patterns of phosphate excretion.

The role of hyperfiltration was examined by reducing GFR experimentally. Reduction in values by as much as 90%, however, generally was associated with only a moderate increase in TRP, and in no instance were values restored to a normal range. Experimental reduction in plasma phosphate concentrations toward normal (and in some animals to below normal levels) evoked an increase in TRP of varying magnitude, but in only one instance (dog 3) was a value approaching the normal range reached. On the other hand, the results of surgical removal of the parathyroid glands were dramatic. In the seven animals studied, before and after thyroparathyroidectomy, the mean value for TRP increased from 55.1% to 88.9%. This postparathyroidectomy value of 88.9% compares quite favorably with the mean value of 92.8% obtained in the diseased kidneys of the five nonuremic dogs studied before removal of the control organs. The rise in TRP, moreover, was not attended by a decrease in GFR; indeed, in two of the seven dogs (dogs 2 and 6, Table V) GFR increased appreciably after parathyroidectomy. Furthermore, in five of the seven postparathyroidectomy studies, plasma phosphate concentrations were 5.4 mg per 100 ml or greater. Thus, the rise in TRP occurred in the presence of persisting hyperfiltration and hyperphosphatemia. The composite data thus point to the parathyroid hormone as the principal effector mechanism in a control system regulating phosphate homeostasis in uremia. The response to parathyroid hormone administration in the parathyroidectomized dogs (Table V) adds weight to this interpretation.

That the low TRP values observed in the azotemic and uremic animals resulted from functional impairment in the residual nephrons seems very unlikely. The fact that TRP values in the diseased kidneys were closely comparable to those of the contralateral kidneys (Table I) would speak against a random defect in phosphate transport in the nephrons of the diseased organs, and the fact that the absolute values for TRP were 85% or greater in these same animals would speak against a major defect in phosphate reabsorption. More compelling evidence is found in the response to thyroparathyroidectomy in the uremic dogs. In three animals, TRP values rose to levels in excess of 90%, and in one animal the value was 98%.

It is concluded that there is a control system that serves to modulate phosphate excretion in advancing chronic renal disease. The afferent limb of this system has not been defined by these studies, but the evidence presented supports the view that parathyroid hormone is the prepotent constituent of the efferent limb, with hyperfiltration of the residual nephrons playing a subsidiary role. Hyperphosphatemia, when present, contributes to an increase in phosphate excretion per nephron.

Summary

These studies were designed to define the basis of the change in the patterns of phosphate excretion that occurs in renal insufficiency. Characteristically, phosphate clearance decreases proportionately less than glomerular filtration rate (GFR); hence TRP, a derived expression for the apparent net tubular reabsorption of phosphate, falls. In animals with unilateral renal disease and a contralateral control kidney, TRP values were not decreased in the diseased kidneys, and there was equality of values in the two kidneys. However, in 27 dogs in which the diseased kidney provided the only source of renal function, the TRP was decreased to a mean value of 48.9%. In seeking the basis for this change, we considered three factors: *1*) hyperfiltration in the residual nephrons, *2*) hyperphosphatemia, and *3*) secondary hyperparathyroidism.

Neither experimental reduction of GFR by as much as 90%, nor lowering of plasma phosphate concentrations, regularly resulted in marked increments in TRP. In contrast, thyroparathyroidectomy was associated with an increase in TRP

from a mean value of 55.1% to 88.9%, and in three of seven dogs values were 93% or greater. The data support the view that there is a control system that governs phosphate excretion in uremia. This system appears to be designed to preserve normal phosphate concentrations in the plasma as long as possible, and it expresses itself by a progressive increase in phosphate excretion per nephron as the number of nephrons diminishes. Of the three major variables that could participate in the efferent limb of this control system, increased parathyroid hormone activity appears to be the most important.

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