STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

XIII. The Effect of Ingestion of Phosphates on the Excretion of Calcium[1]

By RAY F. FARQUHARSON,[2] WILLIAM T. SALTER, and JOSEPH C. AUB

(From the Medical Clinic of the Massachusetts General Hospital, Boston)

(Received for publication November 26, 1930)

Most of the calcium of the body is found combined with phosphate in the skeleton but phosphorus in one form or another is present in relatively large quantities in all body tissue. Any gross change in calcium metabolism must of necessity affect the phosphorus output. It might be possible, however, for considerable changes to occur in phosphorus metabolism without any great effect on the calcium balance.

In the metabolism of bone the two elements are closely associated and under certain abnormal conditions their mutual interdependence is strikingly demonstrated. It has been clearly shown, for instance, (1, 2, 3, 4, 5, 6) that in growing animals the ratio of these two elements in the diet is of the greatest importance and that in the absence of the controlling influence of vitamin D any great departure from the optimal relationship of calcium and phosphorus in the food results in the development of rickets. In the rachitic child or rat, also, Karelitz and Shohl (7) and Shohl and Brown (8) found that the ingestion of added phosphate brought on tetany with the characteristic fall in serum calcium and rise in serum phosphorus.

It is well known that in many conditions there is a definite relationship between the values for calcium and phosphorus in the serum.[3] In

[1] Aided in part by a grant from the Lead Fund of Harvard University.

[2] Alexander McPhedran Research Fellowship in Clinical Medicine, University of Toronto.

[3] The term "serum phosphorus" is used with reference to serum inorganic phosphorus throughout this paper.

tetany, whether infantile, idiopathic, or after parathyroidectomy, the low serum calcium is almost always associated with a high serum phosphorus. A similar relationship was found to exist in terminal nephritis by Marriott and Howland (9), DeWesselow (10), and others. In hyperparathyroidism, on the other hand, whether induced by injections of parathyroid extract or present as a pathological state (11, 12, 13, 14, 15), the serum calcium is high and the serum phosphorus low. In those conditions characterized by low serum calcium and high serum phosphorus the excretion of calcium in the urine tends to be diminished. When, on the other hand, the serum calcium is high and serum phosphorus low, the excretion of both in the urine is increased.

In exophthalmic goiter, Aub, Bauer, Heath, and Ropes (16) found associated with a greatly increased urinary excretion of calcium and nitrogen a corresponding increase in the phosphorus excretion. The converse was found to be true of myxedema. In neither case were serum levels changed appreciably.

It was first observed by Binger (17) that in dogs the injection of large amounts of neutral phosphate caused a marked lowering of the serum calcium with the development of tetany. Tisdall (18) obtained similar results and Salvesen, Hastings, and McIntosh (19) found that ingestion of very large quantities of inorganic phosphate, whether acid or basic, had the same effect. Injection of phosphate in dogs was found by Greenwald and Gross (20) to cause an increased excretion of calcium which persisted for several days. Ingestion of excess phosphorus in children has also been found to result in an increased loss of calcium in the feces (21).

Although such close relationship has been found in the metabolism of calcium and phosphorus, no careful studies have been made of the influence of changes in the phosphorus intake on the calcium metabolism of human adults. The effects noted above, of injection or ingestion of phosphate, were produced in dogs by tremendous quantities which were far in excess of any physiological variation in the phosphorus intake. The purpose of the present investigation was to study the effect of great variations in the ingestion of phosphorus on the calcium balance of adults who had no disorder likely to affect the inorganic salt metabolism. Experiments were planned to differentiate clearly the influence of the phosphate radicle itself from that of the acid or basic properties of its various salts as well as from any possible effect of an increased nitrogen metabolism when the phosphorus intake was increased by feeding a high protein diet.

EXPERIMENTAL PROCEDURE

Most of the patients were given a control diet low in calcium and phosphorus but adequate with respect to other inorganic salts, vitamins, fat, carbohydrate, protein, and total caloric content, as described in a former paper (22). This control diet was so constituted as to give a neutral inorganic residuum when oxidized. When there was of necessity an excess intake of acid radicles, as in a high protein diet, the acid effect was controlled by the administration of an appropriate amount of sodium bicarbonate with each meal. Urine and stools were collected and prepared in three-day periods, as formerly described (22), the specimens for the first three days being discarded. Whenever possible a further nine days was allowed for an initial observation period, nine days for testing each change in regimen, and an after-period of nine days for return to equilibrium before another change was instituted.

METHODS

Calcium determinations were made by Fiske's method (23). This method has been found to be thoroughly dependable and more accurate than methods previously used, especially under conditions when large amounts of phosphate are excreted. Inorganic phosphorus, urinary ammonia, titratable acidity of the urine, and total base, were done by the methods of Fiske and Subbarow; Folin; Henderson and Palmer; and Fiske, respectively, under conditions or minor alterations as previously described (22).

EXPERIMENTS AND RESULTS

The effect of large doses of acid sodium phosphate

WN, a married woman of thirty-four years of age, suffering from chronic atrophic arthritis, was given throughout the whole period of observation the same basal diet low in calcium and phosphorus, and potentially neutral. After a nine-day control period 15 grams of $NaH_2PO_4 \cdot 2H_2O$ was given daily for eight days. Observations were

TABLE 1

Case WN. The effect of acid phosphate administration

Diet	Period	Total acid excretion			Nitrogen		Calcium					Phosphorus				
		Titratable acidity of urine	Ammonia in urine	Titratable acidity + ammonia	Output in urine	Intake	Output			Intake	Balance	Output			Intake	Balance
							Urine	Feces	Total			Urine	Feces	Total		
		cc. N/10	cc. N/10	cc. N/10	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams
Control	I				20.6	27.5	0.24	0.39	0.63	0.29	−0.34	1.13	0.53	1.66	1.85	0.19
	II	193*	550*	743*	21.7	27.8	0.33	0.46	0.79	0.28	−0.51	1.26	0.56	1.82	1.87	0.05
	III	192	556	748	22.0	27.8	0.38	0.54	0.92	0.28	−0.64	1.35	0.64	1.99	1.86	−0.13
Control + $NaH_2PO_4 \cdot 2H_2O$	IV	352	597	949	21.9	28.2	0.36	0.49	0.85	0.28	−0.59	2.18	0.62	2.80	3.85	1.05
	V	1,222	758	1,980	20.0	27.8	0.26	0.55	0.81	0.28	−0.53	7.33	1.62	8.46	10.84	1.88
	VI	870	776	1,646	19.9	27.8	0.33	0.41	0.74	0.28	−0.46	6.77	2.06	8.83	10.84	2.01
Control	VII†	382	956	1,338	14.6	19.0	0.24	0.47	0.71	0.19	−0.52	1.57	0.89	2.46	1.27	−1.19
	VIII	142	914	1,056	17.1	26.4	0.20	0.61	0.81	0.27	−0.54	0.78	0.70	1.48	1.85	0.38
	IX	362	932	1,294	20.5	27.9	0.33	0.67	1.00	0.28	−0.72	1.26	0.76	2.02	1.87	−0.14

* Calculated from one day's results only.

† In period VII patient suffered from an acute upper respiratory infection.

Period IV, 10 grams of $NaH_2PO_4 \cdot 2H_2O$ ingested on last day. Periods V and VI, 15 grams of $NaH_2PO_4 \cdot 2H_2O$ were ingested daily. A constant neutral low calcium diet was eaten daily throughout the observation.

continued for another nine-day after-period. Early in the after-period the patient had an acute upper respiratory infection with a fever of 102°. This condition, however, subsided quickly without having any obvious effect on the excretion of either calcium or phosphorus. It had previously been shown that chronic fevers (16) failed to alter materially the calcium and phosphorus metabolism. The results are given in table 1.

It is quite clear that the ingestion of acid sodium phosphate, in such quantity that the phosphorus intake was increased to more than five times that of the control diet, had no appreciable effect on the excretion of calcium in either urine or feces. The average negative calcium balances for the initial control periods, the periods of administration of acid phosphate, and the final control periods were −0.50, −0.53, and −0.60 grams respectively. It is to be noted also that the increase in the titratable acidity of the urine in response to the ingestion of acid phosphate was much greater than that of the urinary ammonia. Even the slight increase in the ammonia excretion that occurred in this patient on the ingestion of acid phosphate is unusual. It is difficult to explain the further rise in ammonia excretion during the after-period, unless it be in some way associated with the acute infection from which the patient suffered in period VII. It is obviously not related to an increased phosphorus excretion.

Comparison of effects of ingestion of equal amounts of phosphorus as acid and as basic phosphate

In order to distinguish between the effect of the phosphate radicle and that of the acid or basic qualities of its salts, a patient, while maintained on a constant control diet low in calcium and potentially neutral, was given at appropriate intervals about 2.3 grams of phosphorus daily, first as Na_2HPO_4 and then as NaH_2PO_4. RN, a woman of thirty-nine years of age, weighing fifty-six kilos, had suffered from rheumatic heart disease (mitral stenosis), chronic bronchitis, and bronchial asthma. During the period of observation, and for some time before, however, she had no cough, her chest was clear, and there were no signs of myocardial failure. She was comfortable and looked well. In period X, while receiving acid phosphate, she had some

TABLE 2

Case RN. The effect of phosphate administration

Diet	Period	Total acid excretion			Nitrogen		Calcium					Phosphorus				
		Titratable acidity of urine	Ammonia in urine	Titratable acidity + ammonia	Output in urine	Intake	Output			Intake	Balance	Output			Intake	Balance
							Urine	Feces	Total			Urine	Feces	Total		
		cc. N/10	*cc. N/10*	*cc. N/10*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
Control	I				24.1	25.0	0.16	0.21	0.37	0.29	−0.08	1.40	0.50	1.90	1.81	−0.09
	II	531	692	1,223	23.8	25.0	0.11	0.34	0.45	0.29	−0.16	1.33	0.65	1.98	1.81	−0.17
	III	415	598	1,013	23.0	25.0	0.10	0.41	0.51	0.29	−0.22	1.31	0.63	1.94	1.81	−0.13
	IV	526	635	1,161	22.2	15.4	0.14	0.26	0.40	0.18	−0.22	1.36	0.59	1.95	1.16	−0.79
Control + Na_2HPO_4	V	70	306	376	16.6	25.0	0.10	0.32	0.42	0.29	−0.13	3.16	3.33	6.49	8.45	1.96
	VI	−397	313	−84	22.0	22.7	0.10	0.42	0.52	0.25	−0.27	5.32	1.94	7.26	8.60	1.40
	VII	17	276	293	17.7	18.2	0.13	0.41	0.54	0.23	−0.31	5.00	1.28	6.28	8.40	2.10
Control	VIII	306	416	722	16.6	20.5	0.13	0.39	0.52	0.26	−0.26	1.62	0.79	2.41	1.57	−0.84
	IX	180	427	607	18.0	24.5	0.19	0.41	0.60	0.29	−0.31	0.86	0.65	1.51	1.87	0.36
Control + NaH_2PO_4	X*	1,008	697	1,705	19.1	25.9	0.14	0.44	0.58	0.30	−0.28	4.83	2.59	7.42	9.01	1.59
	XI	878	572	1,450	17.5	23.8	0.14	0.30	0.44	0.27	−0.17	5.44	1.32	6.76	8.87	2.11
Control	XII	520	584	1,104	19.9	24.8	0.27	0.42	0.69	0.29	−0.40	2.54	0.75	3.29	1.78	−1.51
	XIII	412	639	1,051	17.8	23.5	0.12			0.26		1.15			1.57	
	XIV	370	611	981	16.8	25.0	0.16	0.40	0.56	0.30	−0.26	0.97	0.66	1.63	1.81	0.15

* Mild diarrhea in period X.

A constant neutral low calcium diet was eaten daily throughout the observation. Periods V, VI, and VII, an average of 10 grams of Na_2HPO_4 were ingested daily. Periods X and XI, an average of 12 grams of NaH_2PO_4 were ingested daily. These represent essentially equivalent amounts of phosphorus.

diarrhea but it ceased after a day or two. Results are presented in table 2.

Again, it can be seen that the ingestion of large doses of phosphate, acid or basic, had no appreciable effect on the excretion of calcium in either urine or stool. When the disodium salt was fed the urine became alkaline and the ammonia excretion fell off but the excretion of calcium remained within the limits found in the initial control periods. On administration of acid phosphate the titratable acidity of the urine rose greatly while the ammonia and calcium excretion remained at basal levels. In both cases, even when there was diarrhea, the great bulk of the phosphate was absorbed and the urinary phosphorus was always much greater than the fecal phosphorus. There was also a marked retention of phosphorus.

The acid effects of NaH_2PO_4

In studying the influence of ingestion of various types of acid-yielding substances on the calcium and phosphorus metabolism, approximately equal amounts of "potential acid" were fed at appropriate intervals, first in the form of foodstuffs, then as NH_4Cl, and later as NaH_2PO_4, to a patient, DA, who was recovering from chronic lead poisoning. He was thirty-seven years of age, weighed thirty-eight kilos, was comfortable, and took his food well and willingly throughout the whole period of observation. The calcium intake was constant and, except during the period when an acid diet was given, the same constant neutral low calcium diet was taken throughout. Results are presented in table 3.

The sum of the ammonia excretion and titratable acidity of the urine is considered here, as in our other work, to give the best indication of the potential acid value of the ingested food or medication. In this experiment approximately equal values for this "total acid" of the urine were obtained during the ingestion of an acid diet, on administration of 4 grams of NH_4Cl daily, and on administration of 2.66 grams of phosphorus in the form of NaH_2PO_4 daily. After the periods in which he received 4 grams NH_4Cl daily the dose was increased to 12 grams per day for two more periods. In response to this large amount of acid ingested there was a very great production of

TABLE 3

Case DA. Effect of ingestion of different types of acid (potentially acid diet, NH_4Cl, and NaH_2PO_4) on calcium excretion

Period	Total acid excretion			Nitrogen		Calcium					Phosphorus					Treatment and remarks
						Output					Output					
	Titratable acidity of urine	Ammonia in urine	Titratable acidity + ammonia	Output in urine	Intake	Urine	Feces	Total	Intake	Balance	Urine	Feces	Total	Intake	Balance	
	cc. N/10	cc. N/10	cc. N/10	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams	grams	
III*	434	563	997	22.6	29.3	0.09	0.53	0.62	0.33	−0.29	1.01	0.89	1.90	2.18	0.28	Last of three initial control periods on fixed neutral low calcium diet
VI	508	1,359	1,867	24.3	49.0	0.18	0.50	0.68	0.30	−0.38	1.44	0.09	2.34	2.89	0.55	Last of three periods on acid diet. 1700 cc. N/10 excess acid
XIII	667	1,631	2,298	28.2	32.2	0.18	0.48	1.66	0.34	−0.32	1.42	0.86	2.28	2.14	−0.14	Last of two periods on fixed neutral low calcium diet plus 4 grams NH_4Cl daily
XV	870	4,787	5,657	36.7	38.7	0.73	0.53	1.26	0.35	−0.91	2.03	0.80	2.83	2.15	−0.68	Last of two periods on fixed neutral low calcium diet plus 12 grams NH_4Cl daily
XVI	259	3,400	3,659	28.0	29.3	0.16	0.83	0.99	0.35	−0.64	0.84	1.19	2.03	2.15	0.12	After-control periods following administration of large doses of NH_4Cl. Patient on neutral low calcium diet
XVII	60	2,543	2,603	24.0	29.3	0.15	0.45	0.60	0.35	−0.25	0.48	0.97	1.45	2.15	0.70	
XVIII	310	1,562	1,872	15.7	29.3	0.23	0.46	0.69	0.35	−0.34	0.46	1.06	1.52	2.15	0.63	

XIX	1,213	1,136	2,349	21.5	29.3	0.07	0.33	0.41	0.33	−0.08	4.57	3.01	7.58	10.14	2.56	Neutral low calcium diet plus 2.66 grams phosphorus as NaH_2PO_4
XX	1,179	699	1,878	21.5	29.3	0.06	0.56	0.62	0.34	−0.28	5.91	3.82	9.73	10.14	0.41	
XXI	295	450	745	21.6	29.3	0.10	0.50	0.60	0.34	−0.26	2.31	1.57	3.88	3.04	−0.84	Neutral low calcium diet
XXII	274	444	718	19.3	29.3	0.07	0.48	0.56	0.35	−0.21	0.86	1.05	1.91	2.15	0.24	
XXIII	245	510	755	20.7	29.3	0.07	0.45	0.53	0.35	−0.18	0.69	1.00	1.69	2.15	0.46	

* The full tables are given in Paper XII (28).

ammonia,[4] and this high level of ammonia excretion persisted on into the after-control period and unfortunately had not yet reached a steady state when the acid phosphate was given, nine days later. The nature of the response to NaH_2PO_4 is, nevertheless, clear.

The different types of acid administered provoked a distinctly different response as reflected in the nature of the increased acid in the urine. It has been pointed out elsewhere (24) that although the total acid output of the urine was approximately equal for the three types of acid ingested, nevertheless, when the acid was given as excess acid in the food or as NH_4Cl, the brunt of the burden was borne by increased ammonia production, and the titratable acidity of the urine was only slightly increased. When acid phosphate was given, however, the titratable acidity increased greatly and the ammonia excretion, still high after the ingestion of NH_4Cl, continued to fall while acid-phosphate was taken. In the second phosphate period it was only slightly higher than that of the control periods.

There was likewise a very great difference in the effect of the different types of acids on the calcium excretion. Those whose ingestion was associated with great ammonia production also gave rise to a considerable increase in the calcium excretion in the urine. The ingestion of NaH_2PO_4, on the other hand, which produced only an increased titratable acidity, was associated not with increased calcium excretion but actually with a slightly diminished output of calcium in the urine. The values for calcium in the feces were little affected by the different types of acid fed, although like those for the urine the lowest values for calcium in the feces of the whole period of observation were obtained during the administration of NaH_2PO_4.

The results of these three experiments show that the ingestion of large amounts of inorganic phosphate, whether acid or basic, fails to influence appreciably the excretion of calcium in either urine or feces in adults on a low calcium diet. The intake of phosphorus in these instances was much greater than could be fed in any diet of natural foodstuffs, corresponding as it did to the phosphorus content of a diet containing well over 200 grams of protein.

[4] That the increased excretion of ammonia which follows on ingestion of NH_4Cl is not due to an increased intake of "ammonia" has been clearly shown in another paper (24). The great excretion of ammonia fell to control levels when an appropriate amount of $NaHCO_3$ was ingested between doses of NH_4Cl.

Effect of food rich in phosphorus

In hyperthyroidism (16) it had been found that a greatly increased excretion of calcium and nitrogen was associated with a corresponding increase in the phosphorus output. To ascertain whether a diet high in protein (i.e. high in phosphorus) would affect the calcium metabolism, 200 grams of protein per day were fed to a healthy normal individual, aged thirty, weighing seventy-eight kilos. In the previous nine days the subject had taken a neutral control diet of approximately the same low calcium content as that of the high protein diet. During the first nine days of the high protein diet sufficient $NaHCO_3$ was taken with the meals to prevent an increase in the "total acid" excretion of the urine, thus eliminating the acid effect of the high protein diet. Results are given in table 4.

On the ingestion of large quantities of protein there was a gradual but definite increase in the calcium excreted in the urine associated with an almost equal decrease in the calcium of the feces, so that the calcium balance for the period of high protein diet plus $NaHCO_3$ was virtually the same as for the control period. The high protein diet had a low residue and during its administration the stools were smaller than formerly although there was no tendency toward constipation. The lower calcium of the stool may be accounted for, in part at least, by the smaller bulk of the feces, as suggested by observations of Sjollema (25). The phosphate of the feces was little increased and after $NaHCO_3$ was discontinued it was actually slightly less than that of the control periods. Phosphorus in the urine increased to over 4 grams, and even on such high intake there was a slight negative phosphorus balance.

The very high protein diet had no appreciable effect on the calcium balance so long as $NaHCO_3$ was taken to neutralize its acid effect. When the $NaHCO_3$ was discontinued the ammonia, titratable acidity, and calcium of the urine all rose but the experiment had to be discontinued before the full effect could be observed.

Moderate calcium diet—Effect of ingestion of added phosphate

All of the previous experiments had been done on patients taking a low calcium diet. The effect of equal amounts of phosphate, first in a

TABLE 4

Case R. F. F. Effect of high protein diet on calcium metabolism

Diet	Period	Total acid excretion: Titratable acidity of urine	Total acid excretion: Ammonia in urine	Total acid excretion: Titratable acidity + ammonia	$NaHCO_3$ added	Nitrogen: Output in urine	Nitrogen: Intake	Calcium: Output: Urine	Calcium: Output: Feces	Calcium: Output: Total	Calcium: Intake	Calcium: Balance	Phosphorus: Output: Urine	Phosphorus: Output: Feces	Phosphorus: Output: Total	Phosphorus: Intake	Phosphorus: Balance
		cc. N/10	*cc. N/10*	*cc. N/10*	*cc. N/10*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
Control	I	521	934	1,455		32.0	28.0	0.29	0.58	0.87	0.34	−0.53	2.11	0.70	2.81	2.08	−0.73
	II	290	854	1,144		27.0	28.0	0.32	0.58	0.90	0.34	−0.56	1.93	0.69	2.62	2.05	−0.57
	III	259	750	1,009		24.0	28.0	0.26	0.55	0.81	0.34	−0.47	1.81	0.66	2.47	2.08	−0.39
High protein + $NaHCO_3$	IV	−265	984	719	2,500	70.0	96.0	0.38	0.54	0.92	0.36	−0.56	3.85	0.74	4.59	4.71	0.12
	V	−28	928	900	3,150	83.2	96.0	0.37	0.54	0.91	0.36	−0.55	4.11	0.93	5.04	4.71	−0.33
	VI	50	1,088	1,138	3,030	89.0	96.0	0.45	0.38	0.83	0.36	−0.48	4.44	0.81	5.25	4.71	−0.54
High protein	VII	238*	481*	2,926		83.1	94.0	0.46	0.32	0.78	0.35	−0.43	4.43	0.62	5.05	4.60	−0.45
		406*	594*														
		492*	716*														
	VIII	494*	714*					0.55					5.22				
		552*	778*														

* Daily determinations.

Periods I–III, control low calcium diet, 58 grams protein. Periods IV–VI, low calcium diet, 202 grams protein plus $NaHCO_3$ to control acidity of protein diet. Periods VII and VIII, low calcium, high protein diet only.

high protein diet and then as added (nearly) neutral inorganic phosphate, was now studied on a patient receiving a moderate calcium intake of about 0.5 gram per day instead of 0.1 gram previously given. LZ, aged eighteen years, weighing sixty kilos, was slowly recovering from chronic multiple neuritis. He was confined to bed throughout the whole period of observation but looked and felt fairly well. After two periods on a diet containing 0.50 gram calcium and 66 grams protein per day he was given a diet of the same calcium content but containing about 120 grams of protein per day. $NaHCO_3$ was added to control the acidity. Later, after an interval of nine days on the control diet, he was given approximately the same amount of phosphorus in an equimolecular mixture of NaH_2PO_4 and Na_2HPO_4. Results are presented in table 5.

The calcium excretion in the urine of this patient was higher than is usual. On an intake of 0.50 gram per day there was in the control periods an average negative calcium balance of 0.44 gram per three-day period. He was kept on the high protein diet for eighteen days, during all of which time he was given $NaHCO_3$. The average value for urinary calcium of the high-protein periods is almost exactly the same as that for the preceding and for the following control periods. During the high protein diet, however, the stools were very much larger than in the control periods, and their calcium content was definitely, although not greatly, increased. There was, accordingly, a greater negative calcium balance during the period of high protein diet. This finding is quite the reverse of that obtained in subject R. F. F. on a high-protein diet. In R. F. F., however, during the ingestion of the high protein diet the stools were smaller than in the control periods. It seems reasonable to attribute the larger output of calcium in the stools of LZ not to any specific effect of increased ingestion of protein and phosphorus but rather to associate it with the greater fecal bulk (due to other causes).

The subsequent administration of 1.1 gram of phosphorus as an equimolecular mixture of Na_2HPO_4 and NaH_2PO_4 resulted in a slight decrease in ammonia and a definite decrease in the calcium of the urine. The size and calcium content of the stools was rather variable but it is clear the administration of inorganic phosphate failed to cause an increase in fecal calcium excretion. The excretion of phosphorus

TABLE 5

Case LZ. Effect of high protein diet and of nearly neutral phosphate

Diet	Period	Total acid excretion: Titratable acidity of urine	Total acid excretion: Ammonia in urine	Total acid excretion: Titratable acidity + ammonia	$NaHCO_3$ added	Nitrogen: Output in urine	Nitrogen: Intake	Calcium: Output: Urine	Calcium: Output: Feces	Calcium: Output: Total	Calcium: Intake	Calcium: Balance		Phosphorus: Output: Urine	Phosphorus: Output: Feces	Phosphorus: Output: Total	Phosphorus: Intake	Phosphorus: Balance
		cc. N/10	cc. N/10	cc. N/10	cc. N/10	grams	grams	grams	grams	grams	grams	grams		grams	grams	grams	grams	grams
Control	I	40	579	619		28.5	39.7	1.04	1.23	2.27	1.54	−0.73	−0.45	1.80	0.61	2.41	2.09	−0.32
	II	94	562	656		30.0	31.7	1.01	0.67	1.68	1.52	−0.16		2.08	0.36	2.44	2.09	−0.35
High protein + sodium bicarbonate	III	279	826	1,105*	1,666	45.6	76.5	0.95	0.83	1.78	1.60	−0.18	−0.87	4.02	0.83	4.85	7.62	2.77
	IV	148	889	1,037	2,142	52.8	62.7	1.20	1.59	2.79	1.55	−1.24		4.61	2.48	7.09	6.15	−0.94
	V	−591	538	−53	2,618	46.1	56.6	0.80	1.38	2.18	1.55	−0.63		4.15	1.69	5.84	5.66	−0.18
	VI	390	1,035	1,425	1,666	47.6	56.6	0.98	1.40	2.38	1.55	−0.83		4.30	2.08	6.38	5.65	−0.73
	VII	−57	814	757	2,142	44.0	48.2	0.99	1.73	2.72	1.19	−1.53		3.51	2.42	5.93	4.83	−1.10
	VIII	−330	738	408	2,142	47.3	53.4	1.11	1.13	2.24	1.41	−0.83		4.66	1.62	6.28	5.29	−0.99
Control	IX	−169	652	483		33.9	32.8	1.00	0.98	1.98	1.38	−0.60	−0.64	2.38	0.60	2.98	2.40	−0.58
	X	−121	608	487		28.5	31.5	1.12	0.87	1.99	1.48	−0.51		2.69	0.52	3.21	2.05	−1.16
	XI	−4	609	605		27.4	31.7	0.91	1.46	2.37	1.55	−0.82		1.98	1.13	3.11	2.09	−1.02
Control + inorganic phosphate	XII	−263	541	278		24.1	31.7	0.86	0.56	1.42	1.52	0.10	−0.39	3.29	0.66	3.95	5.39	1.44
	XIII	113	525	638		20.2	30.7	0.63	2.15	2.78	1.49	−1.29		3.57	1.67	5.24	5.36	0.12
	XIV	70	362	432		16.7	31.7	0.42	1.09	1.51	1.53	0.02		3.28	1.41	4.69	5.39	0.70
Control	XV	−579	406	−173		18.4	31.7	0.76	1.00	1.76	1.52	−0.24	−0.26	1.60	0.50	2.10	2.09	−0.01
	XVI	−241	507	266		20.0	31.7	0.85	0.97	1.82	1.53	−0.29		1.33	0.40	1.73	2.09	0.36

* These varied with the amounts of $NaHCO_3$ ingested.

in both urine and feces was higher on the high protein diet than when the same amount of phosphorus was fed as inorganic phosphate.

In this patient receiving a moderate calcium intake the ingestion of large amounts of phosphorus either in protein or as inorganic phosphorus had produced no great effect on the calcium balance. In his case, however, as in the case of DA, the taking of large amounts of inorganic phosphate was associated with a definite but not great fall in the calcium output in the urine.

Effect of ingestion of phosphate on the serum calcium

In the various experiments blood was taken during fasting just before making a change in phosphorus intake. Under such conditions there was at no time an appreciable change in the serum calcium except that in the case of DA the serum calcium was slightly lowered after ingestion of large doses of NaH_2PO_4.

In one subject blood determinations were made at frequent intervals after a single dose of 3 grams of phosphorus as nearly neutral phosphate. Although the serum phosphate rose from 3.4 mgm. to 5.0 mgm. the serum calcium values were not affected. These results are discussed more fully in another paper (26).

COMMENT

These metabolic studies, with one exception, were made on adults given a diet which was neutral and adequate except in calcium. Wide variation in the ratio of phosphorus to calcium in the intake appears to have but little effect on the excretion of calcium in either urine or feces, or on the calcium balance. Even when the phosphorus intake was increased fivefold the only effect noted was a slight lowering of the calcium of the urine in one case. In the patient studied on a higher calcium intake, the effect of more than doubling the phosphorus intake was similarly negative.

When the acidity of a high protein diet was controlled by the addition of $NaHCO_3$ there was likewise no appreciable effect of such high phosphorus and protein intake on the calcium balance in patients on low or moderate calcium intakes.

The amounts of inorganic phosphorus fed were in general the largest that could be taken without the development of diarrhea. In all cases the stools tended to be a little loose and in one case there was mild diarrhea for a day or so. The absorption of phosphate, however, was good and although phosphorus in the feces was always increased yet it was never nearly so great as that of the urine. Usually about three-fourths of the extra phosphorus output was excreted in urine. When inorganic phosphate was fed there was in all cases definite phosphorus retention. In the two cases on high protein diet there was a slight negative phosphorus balance.

In another paper (27) attention is drawn to the fact that in periods of great phosphate ingestion there was not sufficient total fixed base in the feces to bind the phosphate present as tribasic phosphate, to say nothing of the amount of calcium that would be required to do so. It has been erroneously assumed by some investigators that the Ca/P ratio in the stools can per se be used as evidence for or against the statement that calcium is excreted as a tribasic salt. Under the conditions of our experiments it is quite clear that the ingestion of large amounts of phosphate has had no tendency to increase the elimination of calcium in the feces materially. As to the precise form in which the calcium existed, we have no evidence.

The failure of ingested NaH_2PO_4 to act like other acids in inducing an increased excretion of ammonia in the urine is discussed elsewhere (24). In our experiments, whenever ingestion of acid was associated with definitely increased ammonia production the calcium excretion was also increased. The ingestion of NaH_2PO_4 in all cases resulted in little or no increase in ammonia and no increase in calcium elimination. Increase in ammonia and calcium of the urine are probably separate but parallel responses to the same stimulus. Variation in the ammonia output, however, appears to be the best indication as to the effect of a given "acid" on the calcium excretion. With regard to calcium metabolism, therefore, the acid value of a diet is better measured by its effect on ammonia production than by the "total acid" output (i.e., ammonia plus titratable acidity).

SUMMARY

The effect of large variation of the phosphorus intake, inorganic and organic, on the calcium metabolism of adults receiving a low or moderate calcium intake has been described.

Great variation in the phosphorus intake and, therefore, in the P/Ca ratio failed to affect materially the excretion of calcium in either urine or feces, although in two cases administration of inorganic phosphate resulted in a slight but definite decrease of the calcium of the urine.

Ingestion of a very high protein diet had no appreciable effect on the calcium balance when the acid effect of the protein was controlled by administration of $NaHCO_3$.

Ingestion of NaH_2PO_4 gave rise to a great increase in titratable acidity of the urine but had little effect on the excretion of ammonia or calcium. In this it differed from other acid-producing substances studied, which resulted in increasing both the ammonia and calcium of the urine.

BIBLIOGRAPHY

1. Sherman, H. C., and Pappenheimer, A. M., Proc. Soc. Exp. Biol. and Med., 1921, xviii, 193. A Dietetic Production of Rickets in Rats and Its Prevention by an Inorganic Salt.
2. Shipley, P. G., Park, E. A., McCollum, E. V., and Simmonds, N., Bull. Johns Hopkins Hospital, 1921, xxxii, 160. Studies on Experimental Rickets. III. A Pathological Condition Bearing Fundamental Resemblances to Rickets of the Human Being Resulting from Diets Low in Phosphorus and Fat Soluble A. The Phosphate Ion in its Prevention.
3. McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A., J. Biol. Chem., 1921, xlvii, 507. Studies on Experimental Rickets. VIII. The Production of Rickets by Diets Low in Phosphorus and Fat Soluble A.
4. McCollum, E. V., and Simmonds, Nina, Newer Knowledge of Nutrition. New York, 1929, 4th ed., Chapter XIX.
5. Shohl, A. T., Bennett, H. B., and Weed, K. L., J. Biol. Chem., 1928, lxxix, 257. Rickets in Rats. VII. Metabolism of Calcium and Phosphorus of Rats Fed upon Non-Ricketogenic Diets.
6. Brown, H. B., and Shohl, A. T., J. Biol. Chem., 1930, lxxxvi, 245. Rickets in Rats. XI. The Alteration of Calcium and Phosphorus Metabolism of Normal and Ricketic Rats Produced by Irradiated Ergosterol.
7. Karelitz, S., and Shohl, A. T., J. Biol. Chem., 1927, lxxiii, 665. Rickets in Rats. II. The Effect of Phosphorus Added to the Diet of Ricketic Rats.
8. Shohl, A. T., and Brown, H. B., J. Biol. Chem., 1929, lxxxiv, 501. Rickets in Rats. X. Fasting Tetany and Phosphate Tetany.
9. Marriott, W. M., and Howland, J., Arch. Int. Med., 1916, xviii, 708. Phosphate Retention as a Factor in the Production of Acidosis in Nephritis.

10. DeWesselow, O. L. V., Quart. J. Med., 1922–23 xvi, 341. On the Phosphorus and Calcium of the Blood in Renal Disease.

11. Hannon, R. R., Shorr, E., McClellan, W. S., and DuBois, E. F., J. Clin. Invest., 1930, viii, 215. A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies. Metabolic Study I.

Bauer, W., Albright, F., and Aub, J. C., J. Clin. Invest., 1930, viii, 229. Metabolic Study II.

McClellan, W. S., Hannon, R. R., J. Clin. Invest., 1930, viii, 249. Metabolic Study III.

12. Wilder, R. M., Endocrinology, 1929, xiii, 231. Hyperparathyroidism: Tumor of the Parathyroid Glands Associated with Osteitis Fibrosa.

13. Hunter, Donald, Proc. Roy. Soc. Med., 1929, xxiii, 27. Hyperparathyroidism (Hyperfunction of a Parathyroid Tumor in a Case of Generalized Osteitis Fibrosa).

14. Albright, F., Bauer, W., Ropes, M., and Aub, J. C., J. Clin. Invest., 1929, vii, 139. Studies of Calcium and Phosphorus Metabolism. IV. The Effect of the Parathyroid Hormone.

15. Barr, D. P., Bulger, H. A., and Dixon, H. H., J. Am. Med. Assoc., 1929, xcii, 951. Hyperparathyroidism.

16. Aub, J. C., Bauer, W., Heath, C., and Ropes, M., J. Clin. Invest., 1929, vii, 97. Studies of Calcium and Phosphorus Metabolism. III. The Effects of the Thyroid Hormone and Thyroid Disease.

17. Binger, C., J. Pharm. and Exp. Therap., 1917, x, 105. Toxicity of Phosphates in Relation to Blood Calcium and Tetany.

18. Tisdall, F. F., J. Biol. Chem., 1922, liv, 35. The Influence of the Sodium Ion in the Production of Tetany.

19. Salvesen, H. A., Hastings, A. B., and McIntosh, J. F., J. Biol. Chem., 1924, lx, 311. Blood Changes and Clinical Symptoms Following Oral Administration of Phosphates.

20. Greenwald, I., and Gross, J., J. Biol. Chem., 1925, lxvi, 201. The Excretion of Calcium, Phosphorus, and Magnesium after Injection of Calcium Chloride, Sodium Phosphate, or Both.

21. Orr, W. J., Holt, L. E., Jr., Wilkins, L., and Boone, F. H., Am. J. Dis. Child., 1924, xxviii, 574. The Relation of Calcium and Phosphorus in the Diet to the Absorption of these Elements from the Intestine.

22. Bauer, W., and Aub, J. C., J. Am. Dietetic Assoc., 1927, iii, 106. Studies of Inorganic Salt Metabolism. I. The Ward Routine and Methods.

23. Fiske, Cyrus, and Logan, M. A., To be published in the J. Biol. Chem. First described in a paper by Hamilton, B., J. Biol. Chem., 1925, lxv, 101. Calcium Method.

24. Salter, W. T., and Farquharson, R. F., To be Published. Observations on Urinary Acid and Ammonia Excretion.

25. Sjollema, B., J. Biol. Chem., 1923, lvii, 271. Studies in Inorganic Metabolism. II. The Influence of Crude Fibre and of Protein upon Calcium and Phosphorus Metabolism.

26. Farquharson, R. F., and Tibbetts, D. M., J. Clin. Invest., 1931, x, 271. Studies of Calcium and Phosphorus Metabolism. XVIII. On Temporary Fluctuations in the Level of Calcium and Inorganic Phosphorus in Blood Serum of Normal Individuals.

27. Salter, W. T., Farquharson, R. F., and Tibbetts, D. M., To be Published. The Relation of Acid-Base Balance to Phosphate Metabolism.

28. Farquharson, R. F., Salter, W. T., Tibbetts, D. M., and Aub, J. C., J. Clin. Invest., 1931, x, 221. Studies of Calcium and Phosphorus Metabolism. XII. The Effect of the Ingestion of Acid-Producing Substances.