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Research Article

MAGNESIUM METABOLISM IN HYPERPARATHYROIDISM

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In an earlier, rather extensive, publication in this journal on the "Functional Pathology of Hyperparathyroidism" (1) no mention was made of magnesium metabolism. Data have now been collected permitting a contribution to this phase of the subject. The methods of study were the same as described in the previous paper (1). Magnesium determinations were made by the procedure outlined by Briggs (2).

The pharmacological relationship of calcium and magnesium ions and therefore the necessity for optimum concentrations of both in body fluids suggest a close association of the mechanisms regulating their level in the blood. The fact that magnesium phosphate has solubility properties similar to calcium phosphate and the fairly constant amount of magnesium in bone hint at a specific biological relationship of their compounds.

It would seem that the parathyroid hormone might have at least an indirect influence on magnesium metabolism. The immediate effect of parathyroid hormone on serum magnesium has been studied in dogs by Scholtz (3) and by Greenburg and Mackey (4). Their investigations showed a slight increase in serum magnesium occurring early and before the rise in calcium. By the time calcium had reached maximum values the serum magnesium had fallen towards normal. Our experiments indicated that more prolonged administration of parathormone to dogs resulted in no striking alterations in serum magnesium (Table I). This was also true with rabbits in which parathormone is not very effective in raising the serum calcium.

TABLE I

The effect of continuous parathormone administration on the serum magnesium of dogs and rabbits

	Serum magnesium	
	Before	After
	mgm. per 100 cc.	*mgm. per 100 cc.*
Dog No. 1, parathormone, 50 to 300 units daily for 4 days	3.3	3.4
Dog No. 2, parathormone, 50 to 300 units daily for 4 days	3.0	5.5
Dog No. 3, parathormone, 50 to 100 units daily for 10 days	2.2	2.9
Dog No. 4, parathormone, 50 to 100 units daily for 10 days	2.1	2.9
Rabbit No. 1, parathormone, 10 units daily for 10 days	2.6	1.9
Rabbit No. 2, parathormone, 10 units daily for 10 days	3.2	2.8
Rabbit No. 3, parathormone, 10 units daily for 10 days	2.8	2.9

In clinical *hypo*parathyroidism serum magnesium tends to be lower than the average for normal individuals. This is not a constant or striking phenomenon. Representative values in tetany following thyroidectomy are presented in Table II. For comparison with the *hypo*calcaemia of parathyroid tetany this table also includes observations on patients with *hyper*calcaemia in generalized neoplastic disease of bone, a condition which at least simulates hyperparathyroidism. These patients also showed low normal figures for serum magnesium.

TABLE II

Serum magnesium, calcium and phosphorus of cases with hypocalcaemia and cases with hypercalcaemia

Cases with hypoparathyroidism following thyroidectomy				Cases with hypercalcaemia associated with generalized neoplastic disease of bone			
	Serum				Serum		
	Mg	Ca	P		Mg	Ca	P
	mgm. per 100 cc.	*mgm. per 100 cc.*	*mgm. per 100 cc.*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
Case 11317, Tetany	2.1	8.2	4.4	*Case 22810*, Metastatic	1.9	14.9	2.5
	2.6	7.9	4.7	Hypernephroma	1.9	15.1	2.7
Case 22828, Tetany	1.7	7.6	5.5	*Case C.S.*, Multiple	2.4	13.5	6.8
	1.7	8.8	3.7	Myeloma	1.8	18.1	6.2
Case 23523, Tetany	1.7	7.8	7.7	*Case 27621*, Multiple	2.7	16.5	4.4
	1.8	5.9	5.9	Myeloma	2.0	16.9	4.9
					1.8	16.8	4.0

In *hyper*parathyroidism one finds evidence indicating more clearly that the parathyroid glands have no direct influence on the level of magnesium in the blood. This is illustrated in the studies of a typical case which will later be reported in detail by Olch. The data are recorded in Table III.

Case 26253. This patient, a woman forty years old, had always considered herself healthy. She was raised in the city. Her food habits appeared to have been quite normal. Diphtheria in childhood was the only serious infectious disease she remembered. She was married when seventeen years old. Her only pregnancy was at eighteen years and was apparently quite normal and was followed by an uneventful puerperium. About this time dental caries began to develop and careful cooperation with her dentist failed to save her teeth. Fillings continued to fall out and caries advanced until finally all her teeth were removed. Her weight was continuously around 125 pounds until her hospitalization.

Six years before admission the patient fell on the floor from the level of a bed and broke a clavicle. Three years later she fell on the ice and broke her left humerus. Two years before admission she developed dull pain above her

TABLE III

Indicating the influence of variations in parathyroid activity on serum magnesium

Case 26253. Hyperparathyroidism. A parathyroid adenoma removed January 8, 1931	Serum			Date
	Mg	Ca	P	
	mgm. per 100 cc.	*mgm. per 100 cc.*	*mgm. per 100 cc.*	
Before operation	1.6	16.2	1.9	Nov. 4, 1930
Before operation	1.7	14.0	2.3	Jan. 8, 1931
One day after removing parathyroid tumor	1.7	9.8	1.7	Jan. 9, 1931
Four days after removing parathyroid tumor	1.7	8.3	1.7	Jan. 12, 1931
Seven days after removing parathyroid tumor	1.8	8.9	2.4	Jan. 15, 1931
Eleven days after removing parathyroid tumor	1.9	9.6	2.1	Jan. 19, 1931
Eighteen days after removing parathyroid tumor	2.5	9.5	2.6	Jan. 26, 1931
Three months after removing parathyroid tumor	2.3	10.7	2.4	Apr. 2, 1931
One year after removing parathyroid tumor	2.5	10.2	3.6	Dec. 18, 1931
Case 35690. Parathormone administration to a young woman, normal except for otosclerosis				
Before parathormone	2.2	10.1	3.7	Sept. 20, 1932
After 100 units parathormone in 24 hours	2.6	12.5	2.9	Sept. 22, 1932
After 160 units parathormone in 48 hours	2.7	12.5	2.9	Sept. 23, 1932
After 400 units parathormone in 5 days	2.7	13.4	1.5	Sept. 26, 1932
After 580 units parathormone in 7 days	2.6	12.8	2.3	Sept. 28, 1932
36 hours after stopping parathormone	2.5	10.9	2.5	Sept. 30, 1932
Four days after stopping parathormone	2.5	10.3	3.8	Oct. 3, 1932
Seven days after stopping parathormone	2.6	10.5	3.3	Oct. 6, 1932

left knee. This was thought to be rheumatism, but, when it did not improve after months, an x-ray was taken. Her physician told her there was a lack of calcium in this area and that if she ever broke it healing might not take place. The pain gradually improved.

The patient then felt perfectly well until June 25, 1930, when she stumbled over a hedge and fell on a sidewalk and broke her left femur and right humerus. X-ray examinations showed these to be pathological fractures through multilocular cystic areas in the bone. Further x-ray studies showed similar areas in other bones, especially in the pelvis and upper dorsal spine. X-ray also showed shadows in both kidney regions typical of bilateral nephrolithiasis.

Physical examination disclosed little for comment except moderate emaciation, an upper dorsal kyphosis, hyperactive deep reflexes and a systolic blood pressure of 180 and a diastolic of 100. No tumor in the thyroid region was evident. Blood examinations showed high serum calcium, low serum phosphate, a slight anemia, normal nonprotein nitrogen and negative Wassermann and Kahn reactions. The basal metabolic rate was — 4 per cent. Phenolsulphonephthalein excretion was 70 per cent.

On October 30, 1930, surgical exploration of the thyroid region by Dr. I. Y. Olch disclosed a small tumor, about 1.5 by 2 cm. in size, in the left lobe. After this was removed the serum calcium did not fall and microscopic study showed it to be a foetal adenoma of the thyroid. On January 8, 1931, the neck was explored again and a tumor 1.5 by 4 cm. in size was found lying in a

crevice between the oesophagus and spine and attached by a pedicle to the upper pole of the left lobe of the thyroid. After removing this tumor the serum calcium fell to below normal and the patient experienced moderately distressing symptoms of tetany for about ten days.

Striking improvement in this patient's skeletal abnormalities, as evidenced by x-ray examinations, has followed operation. The improvement in her general condition has been less marked. The bilateral nephrolithiasis opposes a satisfactory course. Although there are no local symptoms, hypertension increases steadily and eventual kidney insufficiency is feared. Her general condition will not permit removal of the stones.

While in the hyperparathyroid state the serum magnesium varied from 1.6 to 2.0 mgm. per 100 cc. These figures are low but within the range of normal variations. Following the removal of the parathyroid adenoma the serum calcium fell typically to values below normal, but this change in state was not attended by any alteration in the level of serum magnesium. During the three weeks following operation magnesium varied from 1.8 to 2.0. Three months later when the calcium was 10.7 mgm. and phosphorus 2.4 mgm. the serum magnesium was 2.3 mgm. per 100 cc. A year after operation the figures were about the same except that the serum phosphorus had risen to normal.

Studies of magnesium, calcium and phosphorus metabolism of this patient, with clinical hyperparathyroidism, are recorded in Table IV. Period 9, the first included in this table, was preceded by eight similar periods in which only the calcium and phosphorus were determined. As in period 9, they showed the typical negative balance of these elements. A definite tendency to lose magnesium in hyperparathyroidism is indicated by the data in this table. A significant relationship to the hyperparathyroid state is emphasized by the change in the magnesium balance which followed the extirpation of a parathyroid adenoma. As the patient was transformed to relative hypoparathyroidism and the serum calcium fell to below normal, the loss of magnesium shifted to a distinctly positive balance. Magnesium was retained as large amounts of calcium and phosphorus were stored. One year after operation the patient was studied for one period on the same diet she was following at home. This contained large amounts of magnesium, calcium and phosphorus, chiefly from milk. The retention of the three elements was still quite marked.

These modifications of magnesium excretion may be secondary to an effect of the parathyroid hormone on calcium or phosphorus of bone. It is interesting to compare the ratios of the balances of magnesium, calcium and phosphorus with the proportions of these substances in bone. Considering calcium as 100, one may calculate the proportions shown in Table V.

It is apparent that a loss of calcium is accompanied by a loss of magnesium and phosphate and that a retention of calcium is accompanied by a retention of the other two elements as might be expected from the

TABLE IV

Magnesium, calcium and phosphorus metabolism of patient 26253 with hyperparathyroidism and the influence of removing the parathyroid adenoma. Also metabolism studies of patient with generalized neoplastic disease of bone and hypercalcaemia. Corresponding serum magnesium, calcium and phosphorus figures are recorded in Tables II and III

4 day periods (1930–31)	Period	Magnesium				Calcium				Phosphorus			
		Intake	Output	Urine	Stool	Intake	Output	Urine	Stool	Intake	Output	Urine	Stool
		grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
Case 26253													
November 4 to 7	9	1.128	1.444	0.539	0.905	14.41	22.51	2.24	20.27	7.00	8.01	5.02	2.99
November 28 to December 1	12*	1.065	1.038	0.634	0.404	11.76	7.04	1.79	5.25	7.02	7.86	5.65	2.21
December 2 to 5	13*	0.993	1.220	0.106	1.115	9.83	13.21	0.73	12.48	7.20	7.76	4.45	3.31
December 6 to 9	14*	1.044	1.136	0.365	0.771	10.29	10.17	0.86	9.31	7.38	6.95	4.88	2.07
December 10 to 13	15*	0.986	1.009	0.157	0.852	11.42	13.36	0.79	12.58	6.39	5.92	3.66	2.26
January 13 to 16	20	0.808	0.679	0.137	0.542	14.00	8.95	0.09	8.86	3.24	1.21	0.20	1.01
January 17 to 20	21	0.883	0.912	0.196	0.716	12.11	10.47	0.04	10.43	3.40	2.02	0.76	1.26
January 25 to 28	23	0.846	0.632	0.076	0.556	12.58	7.25	0.08	7.17	3.20	2.28	1.21	1.07
January 29 to February 1	24	0.827	0.671	0.066	0.605	11.88	3.88	0.09	3.79	3.69	1.74	1.09	0.65
December 17 to 20	25	2.414	1.854	0.554	1.300	15.82	7.51	0.07	7.44	11.25	6.87	4.86	2.01
Case 27621													
January 28 to February 1	1	0.468	0.456	0.175	0.281	2.30	3.06	1.12	1.94	2.64	2.61	1.62	0.99
February 6 to 9	2	0.400	0.391	0.156	0.235	2.11	4.02	1.50	2.52	2.49	2.88	1.99	0.84

* In periods numbers 12, 13 and 14 irradiated ergosterol (Acterol 20 drops t.i.d.) was administered; in period number 15 cod liver oil. Medication may have caused some tendency to retention of calcium and phosphorus.

TABLE V

Ratios of magnesium and phosphorus to calcium

	Calcium	Magnesium	Phosphorus
	grams	*grams*	*grams*
Approximate proportions in bone*	100	2	50
Loss the month before operation	100	7.4	17.6
Retention the month after operation	100	2.3	31.4
Retention one year after operation	100	6.7	53.8

* Analysis of bone from another case of hyperparathyroidism gave the following figures: Calcium 15.39 per cent, magnesium 0.23 per cent, and phosphorus 6.89 per cent. These would give ratios of 100 : 1.5 : 45.

composition of bone. Significant variations from the ratios in bone do occur but further discussion of the data would not be profitable.

A study of a patient with generalized neoplastic disease of bone and hypercalcaemia is included in Table IV (*Case 27621*). This patient showed a markedly negative calcium balance and a slight loss of phosphorus. Nevertheless, she appeared to be in magnesium equilibrium.

Magnesium metabolism was also studied in experimental hyperparathyroidism. A young woman 27 years old, who appeared normal except for moderate undernutrition and otosclerosis, was given 70 to 100 units of parathormone (Lilly) daily for eight days. Magnesium, calcium, phosphorus, nitrogen and sulphur balances were investigated, before, during, and subsequent to the hyperparathyroid state. The results of four day periods of study are summarized in Table V. During the preliminary observations she demonstrated an ability to retain all elements, probably because of an improved dietary regimen. During the eight days of parathormone administration there was a distinct increase in magnesium output, resulting in an evident negative balance. This was due entirely to a rise in urinary magnesium excretion. The serum magnesium rose slightly. When parathormone was discontinued there was a prompt storing of magnesium but no change in the level in the serum. In these observations the mobilization of calcium and phosphorus was quite typical. The excessive phosphorus excretion was greater than could be accounted for by calcium phosphate liberated and the magnitude of the increased protein metabolism. This surplus phosphorus was more than enough to explain the magnesium loss as magnesium phosphate released from the body. In the recovery period the retention of phosphorus could reasonably be accounted for by magnesium phosphate, calcium phosphates, and protein restored.

The negative nitrogen and sulphur balance caused by parathormone may be related to the local inflammatory and slight general febrile reactions caused by the material injected rather than any specific effect of the hormone itself.

TABLE VI

Magnesium, calcium, phosphorus, nitrogen and sulphur metabolism in four day periods of patient 35690, showing the effect of administering parathormone for eight days. Parathormone was given through periods number 2 and 3. The amounts of parathormone and corresponding serum magnesium, calcium and phosphorus figures are recorded in Table III

4 day periods (1932)	Period	Magnesium				Calcium				Phosphorus				Nitrogen				Sulphur			
		Intake	Output	Urine	Stool	Intake	Output	Urine	Stool	Intake	Output	Urine	Stool	Intake	Output	Urine	Stool	Intake	Output	Urine	Stool
		grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
September 17 to 20...	1	0.859	0.821	0.406	0.415	2.74	2.08	0.63	1.45	3.78	3.08	1.96	1.12	35.0	32.4	29.4	3.0	2.76	2.29	2.04	0.25
September 21 to 24...	2 *	0.835	0.871	0.503	0.368	2.68	3.11	1.41	1.70	3.54	5.45	3.25	2.20	30.7	35.1	32.5	2.6	2.19	2.55	2.31	0.24
September 25 to 28...	3 *	0.923	1.184	0.816	0.368	2.84	3.48	1.78	1.70	3.66	5.01	2.81	2.20	35.1	36.6	34.0	2.6	2.85	2.70	2.46	0.24
September 29 to October 2.....	4	0.945	0.862	0.337	0.525	3.37	3.55	0.87	2.68	4.07	3.50	1.75	1.75	34.6	31.6	27.9	3.7	2.79	2.41	2.05	0.36
October 3 to 6.....	5	1.065	0.847	0.444	0.403	3.21	2.91	0.80	2.11	4.34	3.30	2.26	1.04	38.2	31.0	27.3	3.7	3.03	2.41	2.07	0.34

* By accident the stools of periods numbers 2 and 3 were mixed. For convenience of presentation one half of the total was assumed for each period.

CONCLUSIONS

In the hyperparathyroid state there is a negative magnesium balance. Individuals reverting from hyperparathyroidism to normal or the hypoparathyroid state store magnesium. Little evidence was obtained indicating the parathyroid glands have any direct effect on the level of magnesium in the blood. The influence of the parathyroid hormone on magnesium metabolism may be secondary to its action on calcium or phosphorus.

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