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Magnesium Metabolism in Hyperthyroidism and Hypothyroidism *

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In 1939, Hueber (1) reported clinical improvement in patients with thyrotoxicosis after parenteral administration of magnesium. Wiswell (2) subsequently was unable to demonstrate any change in the peripheral metabolism of thyroid hormone in hyperthyroid patients given magnesium sulfate injections, whereas Neguib (3) reported a decrease in size of both toxic and nontoxic goiters and clinical improvement in three thyrotoxic patients given daily injections of magnesium chloride. Tapley (4) demonstrated that the administration of L-triiodothyronine promptly produced negative magnesium balance in two myxedematous patients and called attention to the similarity between the symptoms of thyrotoxicosis and magnesium deficiency, as well as between myxedema and magnesium excess. That the serum magnesium is elevated in hypothyroidism and decreased in hyperthyroidism has long been known (5–7) but has recently been re-emphasized and associated erythrocyte magnesium alterations reported (8).

Dempsey and Astwood (9) demonstrated increased production of thyroid hormone in animals maintained in the cold. Hegsted, Vitale, and McGrath (10) reported that the magnesium requirement to maintain maximal growth rates in animals kept at cold temperatures were four times those of animals kept at normal temperatures. Vitale, Hegsted, Nakamura, and Connors (5) later reported that the growth inhibition caused by the addition of thyroxin to the diet of young rats could be partially overcome by extra supplements of magnesium. Magnesium inhibits the action of thyroxin on uncoupling of oxidative phosphorylation *in vitro*. Conflicting reports exist as to the influence of magnesium deficiency on oxidative phosphorylation (11, 12).

The present investigation was carried out to assess further the relationship between the functional status of the thyroid gland and magnesium metabolism. Hyperthyroid and hypothyroid patients were studied by determinations of serum and erythrocyte magnesiums, exchangeable magnesiums, and by complete balance studies during therapy with propylthiouracil and triiodothyronine, respectively.

Methods

Clinical materials. Eight hyperthyroid and eight hypothyroid patients were studied in our clinical center for metabolic studies. Clinical findings were classical, and the diagnoses were confirmed by determinations of protein-bound iodines, 24-hour ^{131}I uptakes, basal metabolic rates, and, in selected hypothyroid patients, repeat ^{131}I uptakes after the intramuscular administration of thyroid-stimulating hormone. None of the patients had congestive heart failure or were receiving diuretic agents. Two hyperthyroid patients were taking digitalis for control of arrhythmias at the time of referral, and this drug was given in maintenance doses throughout the studies in these two patients. Our clinical center is centrally heated and air conditioned and has a relatively constant temperature of 24° C and relative humidity of 50%. Activity was minimal, restricted to the clinical center, and essentially identical from day to day throughout the course of the studies. Balance studies of 21 to 43 days were carried out in five hyperthyroid patients during propylthiouracil (PTU) therapy and in five hypothyroid patients during triiodothyronine (T_3) therapy. PTU was given each 8 hours in doses of 150 to 200 mg.

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The rate of T_3 dosage increase varied, depending on age, duration and severity of hypothyroidism, and upon the response of the patient to the drug. No untoward cardiovascular manifestations developed during therapy. Determinations of serum sodium, potassium, chloride, calcium, and phosphorus and plasma and erythrocyte magnesium were carried out twice weekly. A blood urea nitrogen and CO_2 combining power were determined once weekly. Exchangeable magnesium determinations were carried out before and after a 4- to 7-week period of therapy. One hypothyroid patient was restudied with a third exchangeable magnesium determination after a 4-month period of thyroxin replacement therapy.

Constant diets and collections. The methods of preparing, storing, and processing constant diets are reported in detail elsewhere (13). Constant diets were given for a 5-day period before starting any collections. Metamucil was given daily to all patients, and distilled water enemas were utilized if necessary to close out fecal collection periods. Sweating was not observed, and no attempt was made to measure sweat electrolytes. Urines were refrigerated during 24-hour collections and samples for calcium, magnesium, and phosphorus acidified to pH 3 with HCl to prevent the precipitation of insoluble salts. Stools were collected in 3-day periods in 1-gallon paint cans and diluted to a predetermined weight with demineralized water. Washed silicate stones were added, and the cans were shaken on a Red Devil paint shaker for 20 minutes. Weighed samples were promptly removed from the homogenized stool.

Analytical methods. Diet and stool samples were subjected to standard Kjeldahl digestion. Sodium and potassium were determined by emission flame photometry. Magnesium and calcium determinations were done on a Zeiss double monochromator flame photometer by the method of MacIntyre (14). Erythrocytes were washed twice with and resuspended in saline, the volume of packed erythrocytes in this suspension was determined for calculation purposes, and a sample of the suspension was subjected to magnesium determinations as above. Phosphorus was determined by a modification of the method of Fiske and Subbarow (15), and nitrogen was done by the method of Ferrari (16). Urinary creatinines and blood urea nitrogens were done on a Technicon autoanalyzer. CO_2 combining powers were determined by the method of Segal (17).

^{28}Mg in the form of $MgCl_2$ was obtained,[1] and specific activity approached 20 mc per g magnesium when received. The material was neutralized with a mixture of sodium bicarbonate-sodium lactate, filtered, diluted to approximately 60 ml with sterile saline, and autoclaved. At zero time, 50 to 150 μc of ^{28}Mg was injected intravenously over a 2- to 3-minute period. Timed serum and urine samples were counted in a 2-channel well scintillation spectrometer employing thallium-activated sodium iodide crystal detectors. Automatic correction of decay of ^{28}Mg (half-life, 21.3 hours) was effected by using a stationary calibrated ^{28}Mg standard in the first channel and counting both channels to its preset count. A direct conversion to microcuries was made by multiplying the counting ratio of the unknown to the standard by the ratio of efficiency of the two detectors and the known microcurie quantity of ^{28}Mg in the standard.

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TABLE I

*Plasma and erythrocyte magnesium values**

Patient	Before therapy		After therapy	
	Plasma	Erythrocyte	Plasma	Erythrocyte
	mEq/L		*mEq/L*	
Hyperthyroid				
O.B.	1.75	4.80	1.70	4.50
M.B.	1.35	5.10	1.60	5.40
V.C.	1.40	5.20	1.75	5.00
O.S.	2.00	4.00	1.75	3.80
F.L.	1.40	4.60	1.75	4.00
E.Sc.	1.42	5.60	1.60	5.00
B.W.	1.40		1.64	
B.B.	1.41			
Mean	1.51	4.88	1.68	4.61
Hypothyroid				
C.K.	2.10	4.80	2.20	5.90
E.S.	1.90	4.40	2.30	4.50
M.Sc.	1.90	4.50	2.00	4.20
M.S.	2.10	5.00	1.80	3.80
L.T.	2.00	5.50	1.75	5.80
M.Sm.	2.00	5.30	1.80	5.00
W.H.	2.30	4.80	1.90	4.40
K.S.	2.12		1.71	
Mean	2.05	4.90	1.93	4.80

* Normal values: plasma, 1.86 ± 0.14 mEq per L; and erythrocyte, 5.29 ± 0.42 mEq per L.

The exchangeable magnesium ($^{28}Mg_E$) in milliequivalents per kilogram at 24 and 48 hours was calculated disregarding fecal loss (since it was found to be insignificant) by the following formula:

$$^{28}Mg_E = {}^{28}Mg \text{ injected} - {}^{28}Mg \text{ excreted (microcuries)} / \text{urinary specific activity (microcuries per milliequivalent)} \div \text{weight in kilograms.}$$

Cellular exchangeable magnesium pools were calculated by the method of Fankushen, Raskin, Dimich, and Wallach (18). Methods of analysis for homogeneity of variances, standard deviations, and t tests are from Bailey (19).

Results

Plasma magnesium values tended to be lowered in hyperthyroidism and elevated in hypothyroidism. PTU or T_3 therapy was associated with shifts of plasma magnesium values towards normal, with the exception of three hypothyroid patients (C.K., E.S., and M.Sc.) who had further elevation of plasma magnesium during T_3 therapy (Table I). Erythrocyte magnesium levels were significantly reduced in only one hyperthyroid patient (O.S.) before therapy and varied unpre-

TABLE II

Average daily urinary and fecal excretion in hyperthyroid patients during propylthiouracil (PTU) therapy

Patient	PTU therapy	Magnesium Excretion Urine	Magnesium Excretion Feces	Magnesium Excretion Total	Magnesium Intake	Calcium Excretion Urine	Calcium Excretion Feces	Calcium Excretion Total	Calcium Intake	Phosphorus Excretion Urine	Phosphorus Excretion Feces	Phosphorus Excretion Total	Phosphorus Intake
		mEq				*mEq*				*g*			
O.B.	Before therapy (9)*	9.87	7.31	17.18	19.80	6.08	31.17	37.25	40.00	0.948	0.464	1.412	1.541
	Day 1 to 10 (10)	8.80	8.68	17.48	18.60	4.60	27.96	32.56	36.67	0.719	0.356	1.075	1.467
	11 to 20 (2)	9.35	9.88	19.23	18.60	4.31	37.50	41.81	36.67	0.800	0.390	1.190	1.467
M.B.	Day 1 to 10 (10)	14.31	10.96	25.27	27.10	13.77	59.86	73.63	84.30	1.32	0.618	1.938	2.399
	11 to 20 (10)	11.22	7.44	18.66	26.80	9.58	40.48	50.06	93.80	1.18	0.538	1.718	2.546
	21 on (6)	10.58	9.45	20.09	27.70	5.40	34.12	39.52	93.80	1.04	0.783	1.823	2.546
V.C.	Before therapy (12)	13.50	11.45	24.95	26.90	9.93	48.12	58.05	63.20	0.927	0.930	1.857	2.170
	Day 1 to 10 (10)	12.26	11.80	24.06	26.90	7.29	59.90	67.19	63.20	0.959	1.072	2.031	2.170
	11 to 20 (10)	11.67	14.77	26.44	31.50	5.18	65.30	70.48	69.60	1.005	1.144	2.149	2.180
	21 on (11)	11.32	14.29	25.61	31.50	3.95	65.27	69.22	69.60	1.161	0.994	2.155	2.180
O.S.	Day 1 to 10 (10)	4.36	5.66	10.02	12.00	4.27	26.26	31.53	51.90	0.764	0.548	1.312	1.22
	11 to 20 (10)	4.20	8.80	13.00	19.40	5.03	59.10	64.13	56.00	0.808	0.788	1.596	1.24
F.L.	Day 1 to 10 (10)	13.04	8.41	21.45	17.60	15.99	29.59	45.58	42.40	0.938	0.439	1.377	1.06
	11 to 20 (10)	6.78	8.45	15.23	17.60	7.66	33.75	41.41	42.40	0.878	0.432	1.310	1.06
	21 on (9)	5.99	9.90	15.89	21.10	7.80	35.28	43.08	46.60	0.927	0.325	1.252	1.45

* Numbers in parentheses represent the duration in days of observations in the respective periods.

dictably after therapy (Table I). No correlation could be made between initial plasma or erythrocyte magnesium levels and the duration or severity of thyroid disease. No abnormalities or significant alterations of serum sodium, potassium, chloride, calcium, phosphorus, blood urea nitrogen, or CO_2 combining power were noted either before or during therapy.

Urinary and fecal excretion of magnesium, calcium, and phosphorus in hyperthyroid patients during PTU therapy and hypothyroid patients during T_3 therapy is shown in Tables II and III, respectively. An analysis of the data from these Tables with excretion expressed as a per cent of intake is found in Table IV. In this Table the hyperthyroid "before therapy" group includes values obtained up to and including the first 10 days of PTU therapy. Hyperthyroid patients excreted a significantly larger amount of ingested magnesium in the urine than hypothyroid patients ($p < 0.01$) before therapy, but these differences disappeared after therapy. The per cent of in-

TABLE III

Average daily urinary and fecal excretion in hypothyroid patients during triiodothyronine (T_3) therapy

Patient	Dosage of T_3	Magnesium Excretion Urine	Magnesium Excretion Feces	Magnesium Excretion Total	Magnesium Intake	Calcium Excretion Urine	Calcium Excretion Feces	Calcium Excretion Total	Calcium Intake	Phosphorus Excretion Urine	Phosphorus Excretion Feces	Phosphorus Excretion Total	Phosphorus Intake
	μg	*mEq*				*mEq*				*g*			
C.K.	Before therapy (3)*	5.23	14.30	19.53	21.30	6.67	22.50	29.17	33.00	0.464	0.200	0.664	1.28
	15 to 30 (3)	8.17	21.00	29.17	21.30	9.07	24.00	33.07	33.00	0.634	0.250	0.884	1.28
	45 to 75 (3)	12.03	18.00	30.03	21.30	11.00	29.30	40.30	33.00	0.941	0.250	1.191	1.28
	90 to 100 (25)	11.34	15.31	26.65	21.30	5.55	30.54	36.09	33.00	0.840	0.316	1.156	1.28
E.S.	Before therapy (6)	7.38	9.79	17.17	18.00	5.72	13.27	18.99	16.00	0.417	0.356	0.773	1.03
	15 to 30 (6)	4.90	9.80	14.70	18.00	5.77	11.62	17.39	16.00	0.634	0.239	0.873	1.03
	45 to 75 (13)	6.52	9.09	15.61	18.00	6.74	17.40	24.14	16.00	0.714	0.457	1.171	1.03
	90 to 100												
M.Sc.	Before therapy (2)	3.45	11.75	15.20	14.00	3.56	21.24	24.80	18.20	0.580	0.200	0.780	0.681
	15 to 30 (6)	5.03	8.57	13.60	14.00	4.25	19.55	23.80	18.20	0.688	0.135	0.823	0.681
	45 to 75 (22)	5.43	9.34	14.77	14.00	5.21	14.74	19.95	18.20	0.687	0.270	0.957	0.681
	90 to 100												
M.S.	Before therapy (3)	3.24	11.03	14.27	11.97	3.68	12.00	15.68	9.20	1.096	0.335	1.431	0.691
	15 to 30 (6)	3.99	6.48	10.47	11.97	4.49	11.72	16.21	9.20	0.817	0.216	1.033	0.691
	45 to 75 (6)	4.52	7.68	12.20	11.97	5.39	12.90	18.29	9.20	0.789	0.262	1.051	0.691
	90 to 100 (7)	4.65	9.94	14.59	11.97	6.61	23.94	30.55	9.20	0.703	0.379	1.082	0.691
L.T.	Before therapy (8)	4.08	9.34	13.42	10.40	7.16	27.96	35.12	26.50	0.511	0.396	0.907	0.750
	15 to 30 (11)	6.49	9.03	15.52	10.40	7.80	17.23	25.03	26.50	0.582	0.382	0.964	0.750
	45 to 75 (15)	7.03	7.92	14.95	10.40	7.88	30.46	38.34	26.50	0.608	0.392	1.000	0.750

* Numbers in parentheses represent the duration in days of observations in the respective periods.

TABLE IV

Analysis of excretion expressed as per cent of intake

Group	Element	Route of excretion	Per cent intake excreted	
			Before therapy	After therapy
Hyperthyroid	Magnesium	Urine	50.9 ± 11.5	36.5 ± 8.4 ($p < 0.02$)*
Hypothyroid			31.2 ± 8.1 ($p < 0.01$)*	46.4 ± 12.7 ($p < 0.05$)* (NS)
Hyperthyroid		Feces	43.7 ± 4.1	43.4 ± 8.1 (NS)
Hypothyroid			77.2 ± 16.1 ($p < 0.02$)	70.0 ± 12.3 (NS) ($p < 0.001$)
Hyperthyroid	Calcium	Urine	16.9 ± 9.7	10.8 ± 4.6 (NS)
Hypothyroid			28.6 ± 9.1 (NS)	40.3 ± 19.0 (NS) ($p < 0.01$)
Hyperthyroid		Feces	73.7 ± 12.7	78.9 ± 26.3 (NS)
Hypothyroid			100.8 ± 24.6 ($p < 0.05$)	126.6 ± 62.1 (NS) (NS)
Hyperthyroid	Phosphorus	Urine	57.7 ± 15.6	56.6 ± 13.6 (NS)
Hypothyroid			77.6 ± 49.8 (NS)	87.1 ± 18.0 (NS) ($p < 0.01$)
Hyperthyroid		Feces	35.4 ± 9.7	38.0 ± 15.4 (NS)
Hypothyroid			36.2 ± 14.8 (NS)	39.1 ± 14.1 (NS) (NS)

* The data have been tested for significance of differences both within and between groups, accounting for p values both horizontally and vertically within groups.

gested magnesium excreted in the urine decreased in hyperthyroids ($p < 0.02$) and increased in hypothyroids ($p < 0.05$) after therapy. The per cent of ingested magnesium appearing in the feces of hyperthyroid and hypothyroid patients did not change significantly during therapy in either group, but those with hypothyroidism excreted a significantly larger per cent of ingested magnesium in their stool both before ($p < 0.02$) and after ($p < 0.001$) therapy than did those with hyperthyroidism. Expressing the data in terms of per cent of total daily magnesium excretion appearing in stool revealed significant differences before (hyperthyroids, 48.9 ± 8.5%; hypothyroids, 71 ± 8.4%, $p < 0.002$) but not after treatment (hyperthyroids, 54.3 ± 8.6%; hypothyroids, 60.3 ± 4.9%, $p > 0.1$). A similar analysis of calcium and phosphorus data revealed statistically significant differences only in the increased fecal excretion of calcium in hypothyroid as compared to hyperthyroid patients before therapy, and in the increased urinary excretion of both calcium and phosphorus in hypothyroid as contrasted to hyperthyroid patients after therapy (Table IV).

TABLE V

Total balance data

Patient	Duration of balance	Weight change	Na	K	Mg	Ca	P	N
	days	*kg*	*mEq*				*g*	
Hypothyroid								
C.K.	34	−3.3	−304.4	−232.1	−178.24	− 87.90	+ 6.33	+ 29.10
E.S.	25	−0.8	+ 45.4	− 98.0	+ 55.90	−132.10	+ 0.63	− 60.55
M.Sc.	30	−9.1	−881.7	−416.5	− 16.90	− 85.30	− 7.21	−151.90
M.S.	22	−9.1	−562.8	−474.0	− 17.80	−264.60	− 9.18	−144.30
L.T.	34	−6.3	−441.8	−232.1	−148.50	−230.50	− 7.34	− 80.79
Hyperthyroid								
O.B.	21	−0.3	+177.1	+274.5	+ 33.32	+ 55.50	+ 5.65	+ 3.62
M.B.	26	+0.7	+421.6	+455.6	+146.10	+868.80	+17.18	+ 82.40
V.C.	43	+2.6	+146.7	+148.8	+167.19	+ 17.28	+ 5.73	+109.82
O.S.	23	+1.1	−164.6	−128.9	+ 87.30	+175.00	− 5.35	+ 4.33
F.L.	29	−0.1	+125.3	−224.7	+ 32.00	+ 10.80	− 3.92	+ 89.76

TABLE VI

*Exchangeable magnesiums ($^{28}Mg_E$) at 24 hours**

	Hyperthyroid					Hypothyroid			
	Before PTU therapy		After PTU therapy			Before T_3 therapy		After T_3 therapy	
Patient	24 hours	48 hours	24 hours	48 hours	Patient	24 hours	48 hours	24 hours	48 hours
	mEq/kg					*mEq/kg*			
O.B.	4.6	4.9	3.7	4.0	C.K.	3.8	4.8	4.9	
M.B.			6.2	8.3	E.S.	3.5	4.2	3.9	4.4
V.C.	4.5	7.0	5.5	6.6	M.Sc.	1.7	2.0	1.5	2.4
O.S.	5.2	6.6	5.0	6.5	M.S.	2.1	2.7	2.6	2.8
F.L.	4.1	4.3	2.8	4.8	L.T.	3.4	4.8	2.8	4.2
E.Sc.	4.7	7.5			M.Sm.	3.1	4.6	2.6	3.2
G.S.	3.9	6.0	3.7	3.9	W.H.	4.6		2.7	
B.B.	5.7	7.8			K.S.	3.2		3.3	
Mean	4.67	6.30	4.48	5.68	Mean	3.17	3.85	3.03	3.40

* Euthyroid = 4.3 ± 0.7 mEq per kg at 24 hours, and 6.4 ± 1.4 mEq per kg at 48 hours.

Over-all balance results are found in Table V, and representative balance graphs for hyper- and hypothyroidism during therapy are found in Figures 1 and 2. In general, during treatment the patients with hyperthyroidism developed positive balance, whereas those with hypothyroidism developed negative balance for all elements checked. Magnesium balance during treatment was invari-

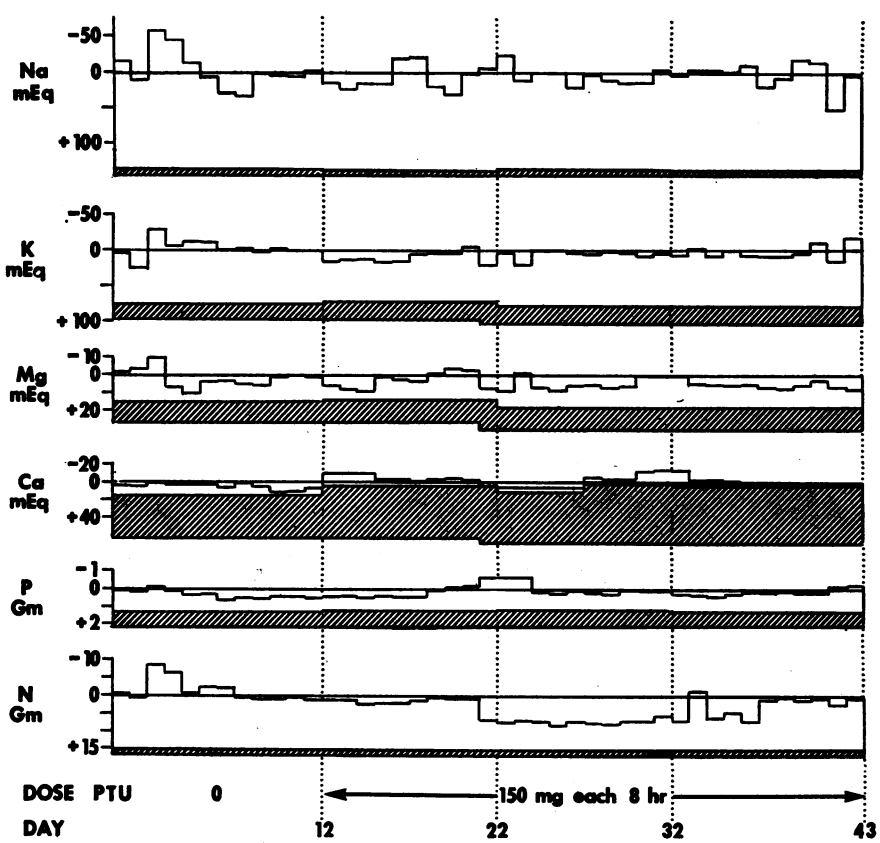

FIG. 1. REPRESENTATIVE BALANCE DATA OBTAINED BEFORE AND DURING PROPYLTHIOURACIL (PTU) THERAPY IN A HYPERTHYROID PATIENT (V.C.). Values above the zero line represent negative balance and those below, positive balance.

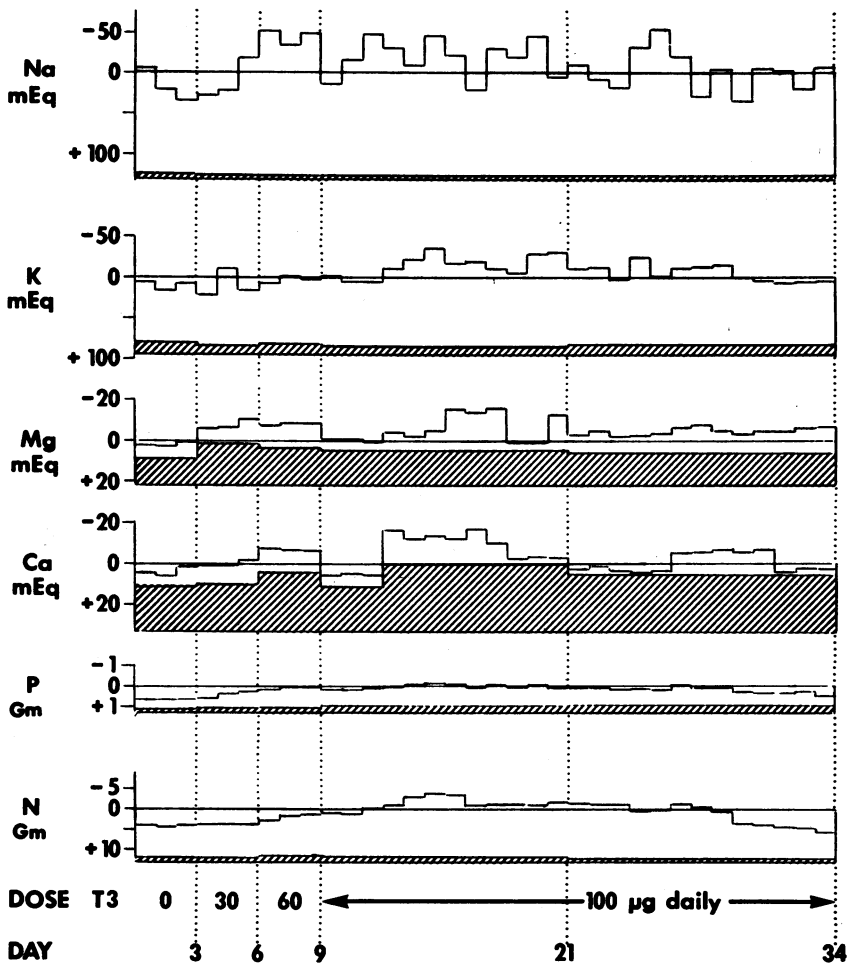

FIG. 2. REPRESENTATIVE BALANCE DATA OBTAINED BEFORE AND DURING TRIIODOTHYRONINE (T_3) THERAPY IN A HYPOTHYROID PATIENT (C.K.). Values above the zero line represent negative balance and those below, positive balance.

ably positive in hyperthyroid patients and, with one exception, negative in hypothyroid patients.

Significant differences in handling ^{28}Mg were noted between the two groups. Hyperthyroid subjects excreted significantly larger amounts of the infused ^{28}Mg in the urine at 12, 24, and 48 hours than did hypothyroid ($p < 0.01$) or euthyroid ($p < 0.05$) subjects. Hypothyroid patients excreted lesser amounts of ^{28}Mg at these time intervals than euthyroids, and the difference was significant ($p < 0.05$) at 48 hours (Figure 3). The urinary excretion of ^{28}Mg decreased after PTU therapy in hyperthyroid patients and increased after T_3 therapy in hypothyroid patients. Exchangeable magnesium values (Table VI) were normal in hyperthyroid patients before, but fluctuated somewhat after, PTU therapy (mean values normal both before and after therapy), whereas low values were obtained in six of eight hypothyroid patients before, and in seven of eight after, short-term T_3 therapy. The one hypothyroid patient restudied after a 4-month period of thyroxin replacement therapy had a normal exchangeable magnesium. No difference in cellular exchangeable magnesium was found between euthyroid and hyperthyroid patients, but hypothyroid patients were observed to have lowered values (Figure 4).

Discussion

Balance studies in hypothyroid patients given widely different doses of T_3 or thyroxin (T_4) by

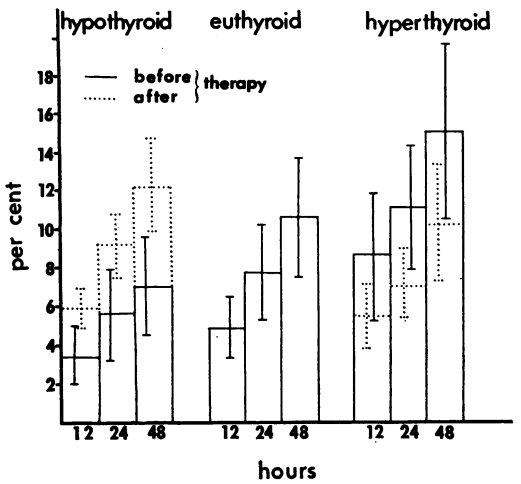

FIG. 3. MEAN (± STANDARD DEVIATION) CUMULATIVE URINE EXCRETION VALUES OF ^{28}MG EXPRESSED AS A PER CENT OF THE ADMINISTERED DOSE IN HYPERTHYROID AND HYPOTHYROID PATIENTS BEFORE AND AFTER PTU OR T_3 THERAPY, RESPECTIVELY. Euthyroid values are shown for contrast.

different routes and for variable periods have been reported by several groups (20–24). Whereas no consistent changes in sodium, potassium, or calcium balances are evident in these reports, nitrogen balance tended to be negative after administration of T_3 or T_4. Munro, Renschler, and Wilson (25), studying exchangeable potassium and sodium, found that PTU or surgical therapy of hyperthyroidism caused an increase in body potassium but no consistent change in sodium content, and therapy of myxedema with T_4 caused a loss of both sodium and potassium. Our results show

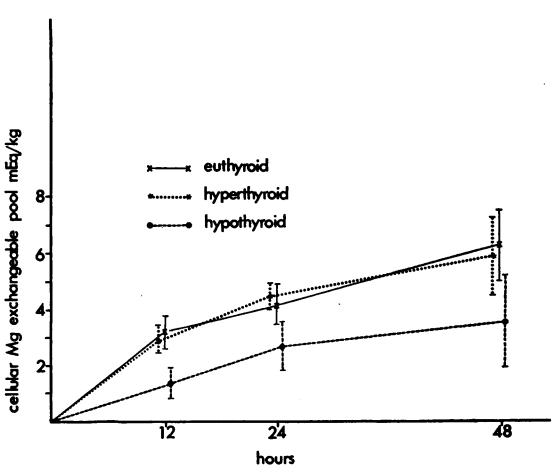

FIG. 4. CELLULAR EXCHANGEABLE ^{28}MG VALUES IN EUTHYROID, HYPERTHYROID, AND HYPOTHYROID PATIENTS.

generally positive balances for sodium, potassium, calcium, phosphorus, and nitrogen in hyperthyroid patients during PTU therapy, whereas hypothyroid patients treated with T_3 had generally negative balances for these elements. Serum sodium, potassium, chloride, calcium, phosphorus, CO_2 combining power, and blood urea nitrogen levels were normal before and showed no significant changes during therapy.

Tapley (4) reported a prompt increase in urinary magnesium excretion after the subcutaneous injections of 1 mg of T_3 in myxedematous subjects. A slight increase in fecal magnesium was also noted but was attributed to variation in fecal volume, since the concentration of magnesium per gram of dry stool remained relatively constant through his study. Cohen (22) included magnesium balances in two of six myxedematous subjects treated with oral T_3 in doses similar to those we employed and found essentially normal magnesium balances. Triiodothyronine therapy in our patients caused a prompt increase in urinary magnesium excretion in four of five hypothyroid patients, but no appreciable change in fecal magnesium excretion (Tables III and IV). A closer analysis of the amount of ingested magnesium excreted in the feces demonstrated a statistically significantly increased excretion in hypothyroid as compared to hyperthyroid patients both before and after therapy (Table IV). Whereas there was a decrease in fecal excretion of magnesium in hypothyroid patients after T_3 therapy, the decrease was not of sufficient magnitude to be statistically different from pretreatment levels. Fecal volume and number of stools per day were greater in hyperthyroid than in hypothyroid patients; thus the increased fecal excretion of magnesium in the latter group cannot be attributed to volume alone. An analysis of fecal calcium excretion showed changes similar to those seen with magnesium, whereas fecal phosphorus excretion was unchanged by therapy and essentially identical in both groups. An analysis of fecal magnesium excretion expressed as a per cent of total daily magnesium excretion showed significant differences between the groups before but not after therapy, suggesting that if our observations had been continued until magnesium balance was achieved the fecal magnesium in hypothyroid patients might have decreased.

Tibbetts and Aub (26) reported positive magnesium balance in two patients with exophthalmic goiter with urine excretions ranging from 19 to 48% and fecal excretions from 27 to 40% of the magnesium intake. Observations before therapy were obtained in only two of our hyperthyroid patients, and both had positive magnesium balances. The negative balances and the increased urine excretion of calcium and phosphorus found by Tibbetts and Aub were not seen in our patients, and none had elevated serum calciums. The positive calcium and phosphorus balance (Table V) during therapy in our hyperthyroid patients is compatible with a negative balance before therapy; the same can be said for sodium, potassium, and nitrogen in most of the hyperthyroid patients studied. Our observations before starting PTU therapy are limited, and the possibility that the balance results might be due to a direct effect of PTU seems unlikely but cannot be excluded.

Consideration must be given to the influence of the magnesium intake and the character of the diet on magnesium balance. Seelig (27) in an exhaustive review of previously published magnesium balance data, concluded that the reported magnesium requirement of 18 to 25 mEq per day (220 to 300 mg) is low and that with intakes below 0.5 mEq per kg per day (6 mg per kg), negative magnesium balance is likely to develop, particularly in men. High intakes of protein, calcium, vitamin D, or alcohol were found to impede retention or to increase the requirement of magnesium, especially in those on low magnesium intakes. That the absorption of magnesium in normal subjects is more avid from diets of low magnesium content is suggested by the ^{28}Mg studies of Graham, Caesar, and Burgen (28). In the patients reported herein, as would be expected, hypothyroid patients selected diets lower in calories as well as protein, calcium, and magnesium than did hyperthyroid patients. One might, therefore, expect to find less of the ingested magnesium appearing in the feces in our hypothyroid than our hyperthyroid patients—an expectation just opposite to our findings. Furthermore, a comparison of our data to composite balance data and graphs of Seelig (27) indicates that our results cannot be explained on the basis of intake alone. The magnitude of negative balance in our hypothyroid patients during therapy exceeds any recorded for normal subjects on similar intakes of magnesium and calcium, and our hyperthyroid patients had strikingly positive balances in contrast to those reported in normal subjects on similar magnesium and calcium intakes. Our experience in normal adults indicates that the intake of magnesium in select diets infrequently reaches levels of 0.5 mEq per kg per day and that magnesium balance is regularly observed with intakes from 0.25 to 0.35 mEq per kg. The fecal excretion of ingested magnesium on intakes in these ranges does not often exceed 60% and is usually lower. Whereas no data exist concerning magnesium losses in sweat in controlled temperature and humidity such as are found in our metabolic study center, Seelig (27) has estimated losses to be 1.25 mEq per day (15 mg per day) under temperate conditions. Although this figure would appear to be maximal to us, accepting such estimates of loss of magnesium in sweat would fail to alter significantly the results of magnesium balance reported.

In 1959, Zumoff, Bernstein, Imarisio, and Hellman (29) reported "departures from the normal pattern" of magnesium kinetics in myxedema but gave no details. Avioli, Lynch, and Berman (30), reporting digital computer compartmental analyses of ^{28}Mg kinetics in thyroid disease, concluded that a selective decrease in exchangeable magnesium existed in "extracellular fluid," "muscle," and "bone" in hypothyroidism. In hyperthyroidism, exchangeable magnesium was selectively decreased in muscle with a two- to threefold increment in flux rates. Propylthiouracil therapy in one hyperthyroid patient was associated with an increase in muscle exchange and a decrease in flux rates. Dimich, Rizek, and Wallach (31) more recently analyzed ^{28}Mg plasma falloff curves and concluded that thyroid hormone stimulates magnesium exchange by altering cellular transport mechanisms.

Total exchangeable magnesiums were normal before and after therapy in our hyperthyroid patients with the exception of minimal elevation in one (M.B.) and reduction in another (F.L.) after PTU therapy (Table VI). The total exchangeable magnesium in hypothyroid patients was low in six of eight before therapy and in seven of eight after therapy. Patient M.S. was restudied after a 4-month period of replacement thyroxin

therapy, and her exchangeable magnesium was then found to be normal (3.87 mEq per kg at 24 hours, 6.39 mEq per kg at 48 hours). We assumed that the explanation for the low post-T_3 therapy magnesium exchanges lies in the short periods of therapy before restudy. Calculations of the cellular magnesium exchangeable pools revealed low values in hypothyroid patients. In contrast to the reports of elevated cellular magnesium exchangeable pools in hyperthyroidism of Fankushen and co-workers (18), we found no difference between euthyroid and hyperthyroid individuals (Figure 4). Aikawa (32), studying magnesium metabolism in rabbits, found a decrease in exchangeable body content of magnesium and a decrease in the relative ^{28}Mg activity in liver and bone after prolonged PTU therapy. Injections of thyroxin in animals caused no measurable changes in magnesium exchange but did result in an increase in the relative ^{28}Mg activity in liver, skin, appendix, and heart. In normal humans, little contribution to the exchangeable magnesium is made by bone (30). It is possible, however, that in the face of hyperthyroidism the contribution of bone to measured exchanges may be larger than suspected on the basis of ^{28}Mg compartmental models utilized to date. The magnitude of positive magnesium and calcium balance we observed in hyperthyroidism during therapy would be in keeping with a significant contribution of bone in the over-all balance. If an increase in rate of flux of magnesium into muscle does occur (30), it is conceivable that the larger dietary intakes of magnesium in hyperthyroidism might function to maintain normal, albeit rapidly exchanging, cellular magnesium levels. The studies of Johnson, Posey, Patrick, and Caputto (33) of ^{32}P incorporation in the muscle of thyrotoxic rats suggest a faster than normal penetration of inorganic phosphorus but an impeded incorporation into organic phosphorus intracellularly. Magnesium transport might similarly be heightened but its intracellular utilization impeded in hyperthyroidism.

It is possible that the mucopolysaccharide of myxedema is capable of polyionic binding and that the negative electrolyte balances seen during therapy are due to the thyroid hormone-induced decreased binding as a result of dissolution of this mucopolysaccharide. Such a hypothesis leaves questions unanswered, at least in relation to magnesium metabolism. The increased excretion of ingested magnesium in the feces, the decreased excretion of magnesium in the urine, and the lowered total and cellular exchangeable magnesium in the face of elevated levels of plasma magnesium strongly suggest that transport difficulties of magnesium across cell membranes occur in hypothyroidism. Known examples of thyroxin influence on transport mechanisms include the thyroxin-induced increase in transport of glucose across the intestine of hamsters (34), the thyroxin-induced increase in water transport across the isolated toad bladder (35), and the thyroxin-induced accelerated cellular penetration of ^{32}P in rats (33).

Summary

Eight hyperthyroid and eight hypothyroid patients were studied by determinations of serum and erythrocyte magnesium, exchangeable magnesium, and total balance studies. Hyperthyroid patients were found to have decreased plasma magnesium, increased urinary excretion of ^{24}Mg and ^{28}Mg, and normal total and cellular exchangeable magnesium before therapy. Hypothyroid patients had elevated plasma magnesium, decreased urinary ^{24}Mg and ^{28}Mg excretion, increased fecal magnesium excretion, and strikingly reduced total and cellular exchangeable magnesium before therapy. Erythrocyte magnesium values were normal in both groups. After propylthiouracil or triiodothyronine therapy, plasma magnesium levels shifted towards normal, and urinary excretion of ^{24}Mg and ^{28}Mg was reduced in hyperthyroid and increased in hypothyroid patients. Total and cellular exchangeable magnesium values remained normal in hyperthyroid and low in hypothyroid patients after short-term therapy. The exchangeable magnesium was found to be normal in one hypothyroid patient restudied after a 4-month period of thyroxin replacement therapy. Over-all balances of sodium, potassium, calcium, phosphorus, and nitrogen during therapy were generally positive in hyperthyroid and negative in hypothyroid patients. Magnesium balance was invariably positive in hyperthyroidism and, with one exception, negative in hypothyroidism. The data suggest that a defect in magnesium transport occurs in thyroid hormone deficiency states.

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