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Magnesium supplementation in protein-calorie malnutrition[1, 2]

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ABSTRACT The widespread observation of magnesium depletion in edematous malnutrition has been confirmed in Guatemalan children. The magnesium requirement during initial stages of therapy has been estimated as 2.7 mEq/kg per day. This may be achieved by adding 0.5% $MgSO_4 \cdot 7\ H_2O$ to a solution containing 15% dextromaltase and 1.5% KCl which is used to dilute whole milk; two parts milk and one part dilution mixture. The replacement of magnesium deficits was not essential for recovery from edematous malnutrition, however, the present evidence suggested that the rate of recovery was accelerated by approximately 2 weeks in those children who received the supplement. *Am. J. Clin. Nutr.* 31: 176–188, 1978.

Magnesium depletion has been reported to occur in protein-calorie malnutrition by numerous investigators (1–15). The lines of evidence are two; the reduced concentration of magnesium in serum (1–6, 8, 14, 16) and tissue (1–4, 8, 11, 12, 15) along with excessive retention of magnesium in balance study (2, 3, 5, 6, 10, 16) and an analysis of clinical benefits in response to magnesium therapy (7, 9, 13, 15). The significance of these findings is obscured by the variability in the observed chemical composition of serum and muscle and clinical response to supplementation. In this report, we determine the quantity of magnesium necessary to meet the deficits present and continuing from admission and evaluate the effect of a magnesium supplement which has been documented to restore serum and muscle composition.

Materials and methods

Children with endematous protein-calorie malnutrition have been studied at the Biomedical Division of the Institute of Nutrition of Central America and Panama (INCAP). The general clinical features of these subjects are identical to those previously described by this unit (17). Informed consent was received from parent or guardian at the time of admission to the metabolic ward.

This study consists of opportunistic observations on magnesium metabolism in children undergoing studies of nitrogen requirements during recovery from malnutrition. An initial group of 12 subjects were described in detail in our 1972 publication (14) on muscle potassium depletion in malnutrition. Because preliminary balance data suggested inadequate magnesium intake, the protocol of clinical management was changed after that study in order to increase oral magnesium intake from 0.12 to 0.42 mEq/kg per day. The clinical description of the 23 additional subjects which make up the magnesium treated group is given in Table 1. Nine of this second study population received from admission, magnesium sulfate injections into the gluteal muscles over a 9 to 23 day period (Table 1). Fatal cases were excluded from the present series.

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TABLE 1
Clinical description of subjects at time of admission

Subject	Age	Weight[a]	Percent of weight/height	Percent of height/age	Infection	Clinical dehydration	History of diarrhea	History of edema	Parenteral magnesium
	mo	*kg*					*wk*		*mEq total/days*
Series I[b] oral magnesium intake 0.12 mEq/kg/day									
179–197	41.5 ± 6	8.5 ± .4	72.5 ± 2.1	85 ± 2	7/12	1/12	6 ± 1	7 ± 1	0/0
Series II oral magnesium intake 0.42 mEq/kg/day									
199	26	7.8	80	83	0	0	4	4	36/8
201	69	11.2	62	81	0	0	8	8	45/10
202	21	4.7	62	78	+	0	12	8	43/20
204	25	7.5	72	87	0	0	0	4	34/16
207	19	6.2	67	87	+	?	2	4	34/16
208	37	8.5	76	84	0	0	4	52	32/16
209	41	8.3	71	84	0	+	35	52	32/16
210	24	9.7	92	94	0	0	4	22	40/19
212	26	6.8	66	86	0	0	1	35	47/22
214	47	8.1	68	83	+	0	5	12	6/2
217	65	11.5	78	85	+	0	1	3	0/0
Mean ± SE	36.4 ± 5.3	8.2 ± 0.6	72.2 ± 2.7	85 ± 1	4/11	1/10	7 ± 3	18 ±.5	31/13
Series III Oral magnesium intake 0.41 mEq/kg/day[c]									
198	39	9.9	94	95			5	18	0/0
200	17	7.2	79	93	+	+	8	16	0/0
215	39	8.5	84	74	0	0	5	40	0/0
216	40	10.4	98	91	+	0	2	5	0/0
218	30	7.6	84	80	+	0	8	12	0/0
219	35	11.3	96	91	+	0		20	0/0
220	52	10.4	87	88	0	0	5	52	0/0
221	19	5.8	62	93	+	+	4	8	0/0
222	49	10.1	93	87	0	0	5	7	0/0
225	34	7.9	83	83	+	0	4	8	0/0
226	32	5.1	74	73	0	+	8	8	0/0
227	45	9.4	90	80	+	0	2	2	0/0
Mean ± SE	35.9 ± 3.1	8.6 ± 0.6	85 ± 2.9	86 ± 2	7/11	3/11	5 ± 1	16 ± 4	0/0

[a] Given weights are minimums following loss of edema. [b] The individual subjects are described in Table 1 of Reference 14, only the summation is recorded here, 12 subjects studied. [c] Not included in Table 4.

TABLE 2
Summary of dietary periods and abbreviations

Dietary period	Abbreviation	Days on diet	Protein intake	Caloric intake
			g/kg/day	*kcal/kg/day*
Admission	A_1	0–1	0	35
	A_2	2–7	0.7	70
	A_3	8+	0.7	70
Therapeutic	T_1	1–7	3.0–4.0	120
	T_2	8–14	3.0–4.0	120
	T_3	15–21	3.0–4.0	120
	T_4	22–28	3.0–4.0	120
	T_5	29–35	3.0–4.0	120
Recovery	R	35+	3.0 +	120+
Admission control[a]	F	10+	0.5–1.0	70

[a] These subjects had all been on the R diet until they had reached 100% of normal weight for height and creatine height index.

As in the previous study (14), the clinical management was divided into two general periods. This dietary protocol is outlined in Table 2. During the admission period (period A), each child received a maintenance diet sufficient to approximate nitrogen balance. The admission diet contained a casein based preparation to provide 0.7 g of protein per kilogram per day and 70 cal per kilogram per day. The patient was kept on the

maintenance diet for 2 or more weeks. As indicated elsewhere, this delayed institution of therapy has been well tolerated (21). At the beginning of the therapeutic period (period T), the dietary intake was adjusted over a four day period so that protein intake was 3 or 4 g and caloric intake was 120 per kilogram per day. The caloric adjustments were made by varying the quantity of sucrose, corn starch, casein, and corn oil in the diet (7). In the first series, the subjects received a dietary supplement of 4 mEq/kg per day of potassium given as a KCl solution separate from the diet and a commercial electrolyte mix was given which provided an additional supplement of sodium, potassium, calcium, magnesium, and sulfate (see prior publication (14)). In the present series, an oral mineral mixture was formulated and given which included the K supplement and which provided 6 mEq K, 1 mEq Na, 0.5 mEq Ca, and 0.42 mEq mg per kilogram per day. A vitamin mixture, as previously described (14), was given daily. All patients received penicillin parenterally for the first 10 days of hospitalization.

The children were also studied at the time of recovery, the R period. This period reflected observations made after more than 50 days on a full therapeutic diet. An additional series (F) was studied when children who had recovered as evidenced by a normal percentage of weight/height and creatinine height index, were placed on reduced protein intakes as part of a separate protocol on protein requirements. Inclusion of these subjects allows an evaluation of the role that nitrogen retention plays in inorganic retentions. Subjects with febrile illnesses or specific gastrointestinal infections were excluded from the present data analysis.

The balance studies were conducted in periods of 3 days marked by carbon or carmine. The results are expressed on the basis of the three day periods. The method of collection of dietary, fecal and urine samples, and analytical techniques have been fully described in prior publications (19, 20). The subjects were at bed rest only during the periods of observation.

A percutaneous needle biopsy technique (18) was used to obtain 10-mg samples of quadriceps muscle for chemical analyses at each dietary subperiod (Table 2). The details of the biopsy procedure and the chemical analyses have been previously published (14, 18, 19). Serum samples were obtained for analyses at the same intervals. The muscle concentrations were calculated with the denominators of fat-free wet weight (FFWW) and fat-free dry weight.

Creatinine excretion was determined by the analytical procedure of Clark and Thompson (22). Both creatinine excretion and weight were adjusted to height and expressed as percent of ideal for height. The adjusted creatinine excretion is referred to as the creatinine height index (23). The anthropometric measurements were referred to the Boston standards. Total serum proteins were measured by refractometry.

The difference between groups was tested with the two-tail Student's *t* test or by analysis of variance. Unless otherwise noted all means are given ± standard error of the mean (SE).

Results

The clinical characteristics of the magnesium supplemented group were identical to

TABLE 3
Clinical response of subjects with protein-calorie malnutrition to magnesium[a]

Diet Period	Days of diet	N[b]	% of weight/height	Series I Without magnesium supplements			N	% of weight/height	Series II and III With magnesium supplements			% of weight/height	Statistical difference (*P* value)		
				CHI[c]	Total proteins	Fecal volume			CHI	Total proteins	Fecal volume		CHI	Total proteins	Fecal volume
						g/3 days					*g/3 days*				
A_1	1	11	80 ± 3	46 ± 3	3.9 ± 0.1	271 ± 73	21	79 ± 2	49 ± 2	4.3 ± 0.2	404 ± 111	NS[d]	NS	0.05	NS
A_2	5	8	80 ± 3	51 ± 5	4.7 ± 0.6	266 ± 112	11	76 ± 2	52 ± 2	4.7 ± 0.2	239 ± 74	NS	NS	NS	NS
A_3	10	8	79 ± 4	47 ± 6	4.4 ± 0.3	88 ± 17	13	74 ± 3	53 ± 3	4.7 ± 0.2	126 ± 22	NS	NS	NS	NS
Therapy															
T_1	5	4	78 ± 7	47 ± 3	5.4 ± 0.4	98 ± 65	14	80 ± 2	59 ± 3	5.8 ± 0.4	93 ± 16	NS	0.025	NS	NS
T_2	10	6	75 ± 2	56 ± 3	6.4 ± 0.3	71 ± 23	13	83 ± 2	68 ± 3	6.7 ± 0.2	121 ± 28	0.05	0.05	NS	NS
T_3	18	2	81 ± 6	70 ± 2	8.0 ± 0.1	80 ± 38	10	87 ± 3	70 ± 2	7.0 ± 0.2	61 ± 10	NS	NS	0.05	NS
T_4	26	6	84 ± 3	80 ± 6	7.4 ± 0.1	120 ± 45	9	91 ± 3	85 ± 3	6.8 ± 0.1	96 ± 34	NS	NS	0.005	NS
T_5	40	4	91 ± 4	82 ± 4	7.5 ± 0.4	171 ± 20	14	97 ± 3	81 ± 2	6.9 ± 0.2	93 ± 20	NS	NS	NS	0.05
Recovery															
R	65, 73	25	100 ± –	91 ± 3	7.3 ± 0.1	138 ± 21	18	104 ± 2	90 ± 2	7.1 ± 0.1	113 ± 19	NS	NS	NS	NS

[a] Mean ± SE. [b] Number of observations in group. [c] Creatinine height index. [d] Not significant.

those of the previously reported group (14) except for a slight but significant difference in percent of ideal weight for subjects in series III (Table 1). The later group had a mean of 82 ± 2 compared to 73 ± 2 and 72 ± 3 in groups I and II, respectively ($P < 0.005$). The historical duration of edema was greater (17 ± 4 weeks) in the supplemented subjects of series II and III than in the unsupplemented subjects (7 ± 1 weeks). All other clinical findings were homogeneous in the total study population.

The clinical response of the supplemented and unsupplemented patients to nutritional rehabilitation is outlined in Table 3. At initial study (A_1), the clinical indices followed were identical except for a small but statistically significant elevation in total serum proteins in the group to receive magnesium supplements; 4.3 ± 0.2 versus 3.9 ± 0.1 g/100 ml, respectively.

In order to differentiate the effects of magnesium supplementation from the therapeutic response to increased protein intake a two-factor analysis of variance was performed (Table 4). In this statistical procedure the subjects in series I and II were divided into periods A, T, and R to discriminate the therapeutic response to protein. They were also divided into those receiving supplemented Mg (series II) and those unsupplemented (series I). The results of this analysis reveal that the only significant factor influencing total serum proteins, CHI and weight/height, was the increase in protein intake following the A period.

The response of the serum and muscle magnesium concentrations of malnourished children to magnesium supplementation is recorded in Table 5. When samples were obtained during the first day of therapy muscle Mg levels were not different from those in the unsupplemented subjects. When samples were obtained the following morning after less than 24 hr of therapy, mean muscle Mg had increased significantly. Serum samples were available from only two of the supplemented subjects during the first hours of therapy. These were 1.64 and 2.60 mEq/liter. In the serum and muscle samples obtained after the first day of diet period A no significant difference could be established between the two routes of Mg administration. The significance of the effect of magnesium supplementation on serum and muscle concentrations is documented in Table 4. Analysis of variance reveals that the level of serum and muscle magnesium is correlated with magnesium supplementation but is independent of the dietary period.

Magnesium balance was significantly affected by supplements of the ion (Table 6). Although the number of supplemented

TABLE 4
Effects of dietary protein and supplementary magnesium on recovery (f/p) two-factor analysis of variance

Dependent variable	Dietary protein	Supplementary magnesium	Interaction
Total serum proteins	195/< 0.001	0.78/NS[a]	1.99/NS
Creatinine height index	149/< 0.001	1.80/NS	0.72/NS
Weight/height index	63.2/< 0.001	0.66/NS	1.21/NS
Serum magnesium	0.89/NS	65.1/< 0.001	2.32/NS
Serum potassium	1.38/NS	1.62/NS	0.83/NS
Serum sodium	0.51/NS	24.9/< 0.001	0.48/NS
Serum chloride	0.30/NS	19.3/< 0.001	1.00/NS
Muscle H_2O%	5.33/< 0.005	0.76/NS	0.24/NS
Muscle Mg/FFWW	2.11/NS	26.9/< 0.001	0.08/NS
Muscle K/FFWW	23.6/< 0.001	8.4/< 0.005	4.80/< 0.01
Muscle Na/FFWW	2.94/NS	0.85/NS	0.56/NS
Muscle Cl/FFWW	7.65/< 0.001	2.75/NS	1.00/NS
Muscle Mg/FFDW	2.30/NS	26.49/< 0.001	0.29/NS
Muscle K/FFDW	7.48/< 0.001	3.85/< 0.05	5.18/< 0.01
Muscle Na/FFDW	9.81/< 0.001	1.26/NS	0.48, NS
Muscle Cl/FFDW	15.12/< 0.001	0.42/NS	0.79/NS
Muscle MFN/FFDW	2.43/NS	43.93/< 0.001	0.25/NS

[a] Not significant.

TABLE 5
Serum and muscle magnesium during recovery from protein-calorie malnutrition[a]

Diet period	Mean days of diet	Series I Without magnesium supplements			Series II and III With magnesium supplements			Statistical difference (*P* value)		
		Muscle mEq/kg FFDW[b]	Muscle mEq/kg FFWW	Serum mEq/liter	Muscle mEq/kg FFDW	Muscle mEq/kg FFWW	Serum mEq/liter	Muscle FFDW	Muscle FFWW	Serum
Admission										
A_1	0	90 ± 22 (9)[c]	14 ± 3 (9)	1.29 ± 0.09 (9)	76 ± 12 (5)	14 ± 2 (5)	2.12 ± 0.48 (2)	NS[d]	NS	0.01
	1	75 ± 17 (3)	17 ± 6 (3)	1.47 ± 0.17 (3)	162 ± 18[e] (16)	32 ± 4[e] (16)	1.85 ± 0.10 (14)	0.05	NS	NS
A_2	5 ± 1	93 ± 22 (10)	18 ± 4 (9)	1.33 ± 0.07 (9)	118 ± 21 (6)	22 ± 3 (6)	1.65 ± 0.17 (6)	NS	NS	0.05
A_3	10 ± 1	130 ± 25 (6)	22 ± 6 (6)	1.12 ± 0.11 (9)	156 ± 26 (15)	28 ± 4 (15)	1.97 ± 0.12 (9)	NS	NS	0.005
Therapy										
T_1	5 ± 1	104 ± 69 (2)	18 ± 12 (2)	1.11 ± 0.11 (6)	119 ± 25 (13)	27 ± 6 (13)	1.71 ± 0.13 (10)	NS	NS	0.005
T_2	10 ± 1	95 ± 16 (8)	18 ± 3 (8)	1.19 ± 0.09 (11)	206 ± 50 (10)	41 ± 9 (10)	1.79 ± 0.11 (12)	0.05	0.025	0.005
T_3	18 ± 1	70 ± 32 (3)	14 ± 6 (3)	1.21 ± 0.16 (7)	141 ± 20 (10)	28 ± 4 (10)	1.78 ± 0.13 (11)	NS	NS	0.01
T_4	26 ± 1	67 ± 13 (8)	14 ± 2 (8)	1.27 ± 0.11 (8)	186 ± 63 (8)	37 ± 3 (16)	1.64 ± 0.08 (7)	NS	NS	0.005
T_5	40 ± 3	74 ± 10 (4)	17 ± 4 (13)	1.47 ± 0.06 (6)	155 ± 27 (15)	29 ± 5	1.75 ± 0.10 (15)	NS	NS	NS
Recovery										
R	65 ± 4, 73 ± 4[e]	60 ± 7 (14)	12 ± 1 (14)	1.36 ± 0.07 (12)	126 ± 14 (18)	24 ± 3 (18)	1.65 ± 0.08 (17)	0.005	0.005	0.01

[a] Mean ± SE. [b] Fat-free dry weight. [c] Number of observations in group. [d] Not significantly different by *t* test. [e] Significantly different from previous biopsy (*P* 0.01 or less).

TABLE 6
Magnesium balances during recovery from protein-calorie malnutrition[a]

Dietary period		Days on diet	Weight	Magnesium intake	Fecal magnesium	Urinary magnesium	Retained
			kg				
A	Without Mg supplements	6±1 (19)[b]	9.8±0.5 (19)	3.6±0.7 (19)	3.7±0.3 (19)	1.5±0.3 (19)	3.4±0.6 (19)
$T_{1,2}$	Series I	11±1 (21)	9.2±0.4 (21)	10.4±0.9 (21)	6.0±0.7 (21)	1.5±0.4 (21)	2.9±1.3 (9)
T_5		59±2 (9)	10.8±0.7 (9)	30.0±3.7 (9)	22.9±4.3 (9)	24.0±0.5 (9)	4.7±2.3 (9)
R		163±11 (24)	14.3±0.4 (24)	42.7±3.9 (24)	22.9±2.9 (24)	9.0±1.2 (24)	10.8±2.7 (24)
F		205±15 (6)	15.7±0.4 (4)	26.6±8.8 (6)	9.6±3.7 (6)	13.1±3.0 (6)	5.0±2.7 (6)
A	With Mg supplements	5±1 (6)	9.1±0.8 (6)	61.6±1.3 (6)	27.7±2.3 (6)	16±1.9 (6)	17.9±1.6 (6)
$T_{1,2}$	Series II and III	9±4 (4)	10.9±0.2 (4)	62.4±8.7 (4)	35.3±7.3 (4)	8.2±2 (4)	19.1±6.3 (4)
T_5		43±2 (2)	12.8±0.1 (2)	76.6±1.6 (2)	29.6±4.4 (2)	15.1±0.5 (2)	31.9±2.3 (2)
A	Statistical difference between Mg groups (*P* value)	NS[c]	NS	<0.005	<0.005	<0.005	<0.005
$T_{1,2}$		NS	NS	<0.005	<0.005	<0.005	<0.005
T_5		<0.005	NS	<0.005	NS	<0.005	<0.005

[a] mEq/3 Days mean ± SE (N). [b] Number of balance periods. [c] Not significant.

magnesium balance observations was small in comparison to the balance studies done in unsupplemented subjects, as would be expected, retentions were five to six times greater ($P < 0.005$) in the supplemented subjects during the A and T periods. No observations were available on the effect of magnesium supplements on the balance of this ion in recovered subjects. The observations on unsupplemented recovered subjects are useful in evaluating minimal magnesium requirements in a subsequent section of this report. There is a relationship between muscle, serum magnesium concentrations, and balance retentions. Retentions less than 0.16 mEq/kg per day were associated with failure of the maintenance of muscle and serum concentrations in the A and R periods (Table 7).

To evaluate the nutritional significance of magnesium supplements during rehabilitation, an analysis has been made of the effect of supplements on serum and muscle electrolyte composition. A table giving the analytical data from serum and muscle electrolyte analyses is available by request from the authors or The Houston Academy of Medicine Texas Medical Center Library. As previously noted in Table 5, serum and muscle magnesium concentrations were increased when magnesium was supplemented. The remaining serum and muscle concentrations are not different throughout the A period in the two groups of subjects. The supplementation with magnesium was not effective in restoring the altered electrolyte compositions during the two week admission (A) period.

The disordered muscle electrolyte and water concentrations returned to normal when the children were treated for their underlying malnutrition (T period). By the T_{3-4} period, muscle potassium concentrations returned to normal in the subjects supplemented with magnesium. This occurred in T_5 period of the unsupplemented. The return of muscle water, sodium and chloride concentrations to normal was not affected by the magnesium supplementation. The myofibrillar fraction of muscle nitrogen increased during the T_{3-4} period in the supplemented children but not until the T_5 period in the unsupplemented subjects.

An analysis of the significance of differences between the magenesium supplemented and unsupplemented groups of subjects in the three dietary periods appears in Table 4. Muscle water, chloride and sodium concentrations were related to dietary period and independent of magnesium intake. The differences in sodium concentrations were evident only on a fat-free dry weight basis. Muscle potassium was most significantly associated with dietary protein intake, however, it was also significantly correlated with magnesium supplementation.

Magnesium supplementation did not alter nitrogen, potassium, or sodium retention in the A period. A table giving the analytical data from balance studies of nitrogen, potassium, and sodium is available from the authors or from The Houston Academy of Medicine Texas Medical Center Library. On identical intakes, nitrogen retention was reduced in the supplemented group at the time of final study; retention remained high in the unsupplemented subjects. On a constant intake, potassium retention was increased by three-fold by the provision of supplementary magnesium during the T period. This difference in retention remained at the time of the R period studies. Sodium retention paralleled potassium retentions in the two groups.

TABLE 7
Relation between magnesium retention and body composition[a]

Diet period		N[b]	Magnesium retention	Serum magnesium		Muscle magnesium	
				Initial	Final	Initial	Final
			mEq/kg/day	*mEq/liter*		*mEq/kg FFDW*	
A	Without supplement	9	0.161 ± 0.089	1.19 ± 0.07	1.08 ± 0.08	126 ± 27	84 ± 15[c]
	With supplement	3	0.692 ± 0.236	1.27[d]	1.92 ± 0.26	74	183 ± 42[c]
F	Without supplement	6	0.161 ± 0.169	1.22 ± 0.07	0.97 ± 0.07	91 ± 17	69 ± 9

[a] Mean ± SE. [b] Number of observations in group. [c] Significant at $P < 0.025$. [d] Two samples lost.

Discussion

In 1968, a revision was made in mineral supplements given to children under therapy for edematous malnutrition in the Biomedical Division if INCAP. Observations made before and after this alteration of electrolyte supplements allow an evaluation of the possible role of magnesium supplementation in the treatment of this disease. Magnesium intake was increased from 0.12 mEq/kg per day by mouth to 0.42 mEq/kg per day by mouth, supplemented with intramuscular magnesium sulfate injections. The intramuscular injections provided an additional total of 35 ± 4 mEq during the equilibration of period A. The dietary management of the patient was otherwise unchanged during rehabilitation.

The revision in magnesium supplementation was the result of initial balance studies performed in 1967 which indicated very low retentions. This was confirmed by the presence of low serum and muscle magnesium concentration which frequently were further depressed during rehabilitation. These data are summarized in Tables 5 and 6. The opportunistic observations on the lower magnesium intake allow the estimation of the minimum magnesium requirements. The possible benefits of the higher magnesium intake will be discussed in a subsequent section.

Evidence for magnesium deficiency

The distributions of serum and muscle magnesium concentrations at admission and recovery are presented in Figure 1 where the data have been grouped according to magnesium supplemented status. Less than 10% of the supplemented children had serum values below 1.3 mEq/liter. Fifty percent of the serum magnesium values at admission and recovery in the unsupplemented children fell below this value. Approximately 12% of the supplemented subjects had muscle values less than 10 mEq/kg FFWW. In the unsupplemented subjects, 50% of muscle magnesium concentrations were less than 10.

The responses to magnesium supplementation are exemplified by the patients whose serial observations are recorded in Figure 2. The presence of high muscle magnesium

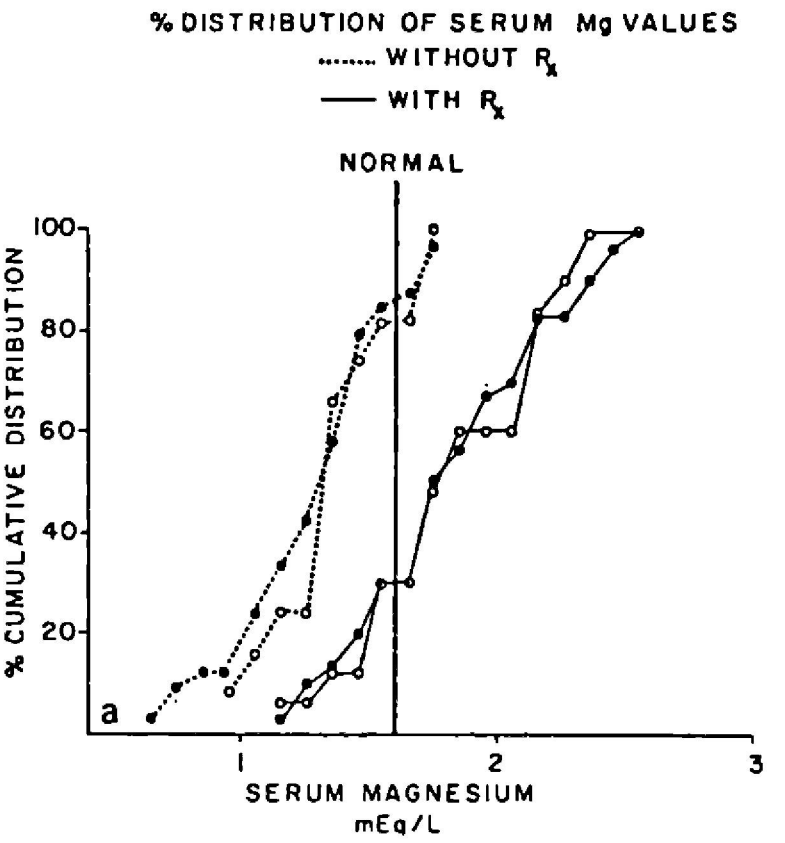

FIG. 1. Cumulative distributions of serum (a) and muscle (b) magnesium concentrations in the A (admission, *closed circles*) and the T (therapeutic, *open circles*) dietary periods. The supplemented subjects are indicated in *solid lines*. The *vertical lines* are the normal values from this laboratory. They are not matched for age and, therefore, only serve as a relative reference.

concentrations in some of the magnesium supplemented children was a surprise. The correlations that exists between serum and muscle concentrations (muscle Mg, mEq/kg FFWW = serum Mg, mEq/liter · 16.5 −3.5; r = 0.412; n = 158) indicates that this is not due to a methodological error in muscle chemical analyses. High values of muscle and serum magnesium have been

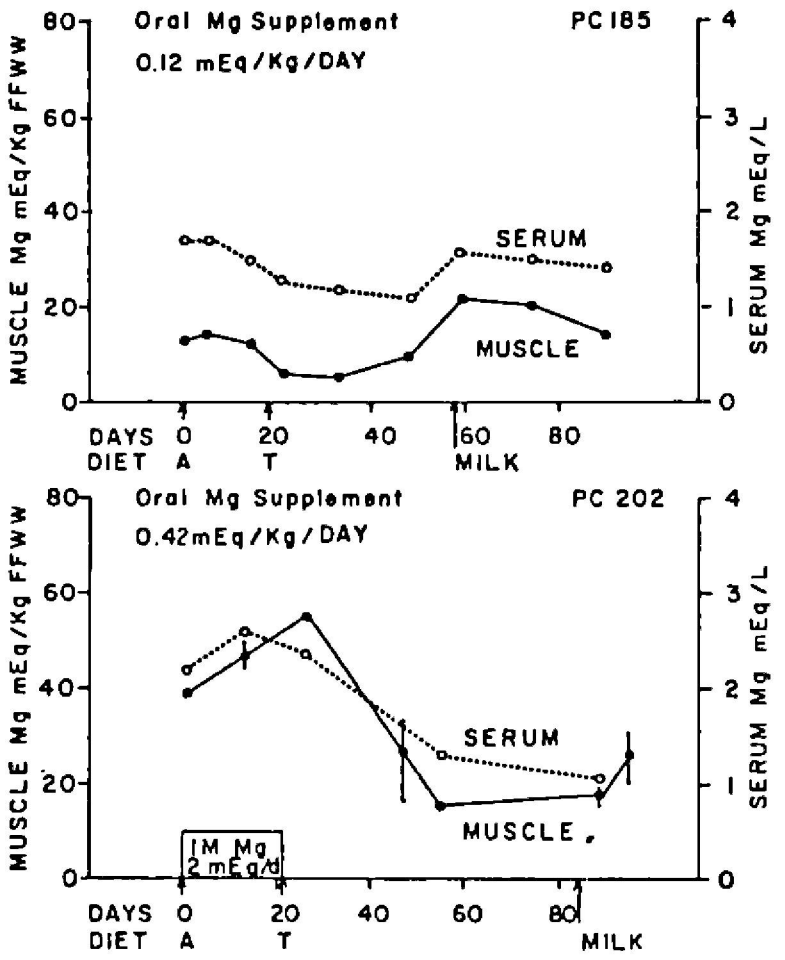

FIG. 2. Serial observation of serum and muscle magnesium concentrations in individual subjects receiving two levels of magnesium intake during recovery from protein-calorie malnutrition. The dietary periods are indicated at the bottom of each panel. Protein intake was 0.7 g/kg per day during the admission (A) period and 3 g/kg per day during the therapeutic (T) period. Serum values are indicated by *open circles* and muscle by *closed circles*. In addition to the oral supplement subject PC 202 received 2 mEq/day of intramuscular magnesium during the first 21 days of hospitalization. This began 18 hr before the first study. Duplicate muscle samples were obtained from patient 202 on several occasions. The magnesium concentrations of these duplicate samples are indicated by the *vertical bars* in this panel in order to illustrate the relative precision of the sampling technique.

reported in rats subjected to protein calorie deprivation (24), adrenalectomy (25–27), or magnesium injection (25). It is not known whether these animal studies apply to these observations in children, however, they present a precedence for these observations. It is possible that the reduced renal function (21) present in our patients contributed to the observed elevations of serum and muscle magnesium concentrations.

The large variability of magnesium concentrations at admission and throughout recovery in these malnourished children is similar to that in previous reports. Figure 1 clearly indicates that these concentrations do not follow a Gaussian distribution. These data, when combined with the non-parametric proof of response to supplementation (Table 4), document a high prevalence of magnesium deficiency in these subjects.

Therapeutic requirements of magnesium

On-going renal excretion. In the pioneer studies on magnesium retention in normal children, Macy (28) found that there is a renal excretion of approximately 30% of magnesium ingested. This was observed in the present study. A regression equation derived from all urinary magnesium excretions in relation to the quantity of magnesium absorbed or administered by injection reveals that urine magnesium (mEq/3 days) is equal to 0.1 mEq/3 days plus 0.34 times the absorbed magnesium (mEq/3 days). The correlation coefficient is 0.780 for 66 observations in all dietary periods. The slope of the regression equation indicates that regardless of absorbed dose, on the average, a third of the magnesium available for retention will be excreted.

Gastrointestinal absorption. Macy (28) found that 54% of oral magnesium was lost in the feces. Lindner et al. (5) report that these losses are increased in malnourished children because of the diarrhea commonly present at admission. This group of investigators reported a relationship between fecal weight and percent magnesium absorption such that magnesium absorption (percent) equals 32.4% minus 0.235 times fecal weight in g/kg per day ($r = 0.41$). In the present investigation, this relationship is confirmed; percent magnesium absorption equals 50% minus 0.043 times fecal weight in grams per 3 days. The correlation coefficient in this study is 0.45 for 77 observations. The equation would predict that as fecal volume increased to 30 g/kg per day, magnesium absorption approached zero. In the present study such losses were observed in only one subject who had unusually severe diarrhea with fecal volumes between 80 and 110 ml/kg per day.

A stronger statistical relationship exists between total mangesium intake and fecal losses. The relationship is defined by a regression equation: Fecal magnesium mEq/3 days equals 0.17 mEq/3 days plus 0.53 times dietary magnesium, mEq/3 days.

The relationship is highly significant (r = 0.86). The slopes and correlation coefficients are identical in all three dietary periods. The slope of the relationship confirms Macy's estimate (28) of 46% net absorption of dietary magnesium.

Insensible losses. In prior investigations (21), we have shown that a significant proportion of nutrients "retained" in balance studies are actually lost insensibly. We have presented evidence for the validity of this concept for nitrogen, potassium, and sodium retentions. It is thought that these insensible losses occur through desquamation. An indirect estimate of the magnitude of insensible magnesium losses is possible based upon apparent retentions when subjects were on a marginal nitrogen intake which resulted in static body composition. These data are presented in Table 7. During the A period, the "retention" of magnesium averaged 0.16 ± 0.09 mEq/kg per day. In recovered subjects fed the same nitrogen intake (F period), the "retention" was 0.16 ± 0.17 mEq/kg per day. Body weight was static in both groups, therefore, growth requirements were nil. On these intakes there was a reduction of serum and muscle magnesium concentrations indicating that the level of retention did not maintain body composition and is therefore probably lost insensibly. Recovery of serum and muscle magnesium concentrations always occurred when retentions exceeded 0.4 mEq/kg per day. For these reasons, a requirement of 0.16 mEq/kg per day is taken as a minimal estimate of insensible losses, however, the true requirement lies between this and 0.4 mEq/kg per day.

Requirements to meet deficits. An estimate of body magnesium deficits can be obtained by comparing the retentions during A period with those in the R or recovery period. The relationship between magnesium absorption and retention at admission is described by the regression equation, retained magnesium, mEq/3 days = 0.50 + absorbed magnesium mEq/3 days × 0.84 (r = 0.85). In the R period, the equation is: retained magnesium = −4.35 + absorbed magnesium × 0.79 (r = 0.88). The slopes of the two groups of observations are similar. Covariant analysis reveals that retention during the A period is significantly greater ($P < 0.001$) than that in the R period. This averages 4 mEq/3 days retention in excess of that in the R period; a retention of 0.30 mEq/kg per day in excess of that in the recovered child who is undergoing rapid growth. The data derived from comparison of regression analyses underestimates the retentions to meet deficits because they include retentions for growth during the R period, 0.14 mEq/kg/day (see below) which were not present during the A period.

Growth retention. The retention of magnesium during times of growth is composed of insensible loss and retention in new tissues. Using the figure for insensible loss of magnesium derived earlier, the portion of retention due to growth can be determined. The unadjusted retentions in periods T and R are 0.28 ± 0.38 and 0.29 ± 0.41 mEq/kg per day. When corrected for average insensible losses, growth retentions are 0.13 ± 0.40 and 0.14 ± 0.40 in the T and R periods, respectively. The relationship between nitrogen and magnesium balance is confirmed by an analysis of magnesium retentions in relation to nitrogen retentions. If less than 50 mg/kg per day of nitrogen was retained, magensium retention was equivalent to insensible losses, 0.14 ± 0.2 mEq/kg per day. In the presence of larger nitrogen retention, 0.35 ± 0.41 mEq/kg/day of magnesium was retained ($P < 0.005$).

Total magnesium requirements. The insensible loss, deficit retention and growth retention of magnesium appear to have finite dimensions; 0.16, 0.54, and 0.14 mEq/kg per day, respectively. The renal and fecal losses vary according to absorption and ingestion respectively. In order to meet the fixed requirements, allowances for obligatory renal and fecal losses must be made. Summarizing the insensible, deficit and growth requirements, the requirement for oral therapy must be adjusted for 47% absorption and 66% availability for retention, 0.84 mEq/kg per day times (1 ÷ (.47 × .66)) is 2.7 mEq/kg per day at admission. Of this requirment, 1 mEq/kg per day is dedicated to the sensible and insensible ongoing losses and growth requirements. This

is the minimum to prevent further depletion. An additional deficit requirement, up to 1.7 mEq/kg per day is required, depending on the desired speed of repletion. The relevance of these oral requirements is exemplified by the magnesium content of whole cow's milk which, when taken in the usual quantity, provides a magnesium intake of 1.2 mEq/kg per day. This can provide for minimal requirements, but is insufficient for deficit therapy. An additional supplement of up to 1.7 mEq/kg per day is required if the total deficit is to be replaced during rehabilitation with whole cow's milk. Because of the increased efficiency of parenteral supplements, the deficit can be met by the parenteral supplementation of much smaller quantites of magnesium up to 0.7 mEq/kg per day depending upon the desired rate of deficit replacement. Lesser amounts are quite adequate, the magnesium supplemented subjects received a total of 2.25 mEq/kg per day, of which 0.25 to 0.5 mEq/kg were received by parenteral injection. This was associated with a retention of 0.66 mEq/kg per day. This level of retention was associated with restoration of serum and muscle concentrations and, as will be discussed below, possible evidence of clinical benefit. From this analysis, it is certain that the original series of subjects received inadequate magnesium during initial therapy and that the supplemented subjects reported in the present paper received adequate, if not optimal, magnesium intake.

Effects of magnesium supplementation

Having established that the supplementary magnesium given to the study subjects of the present report was sufficient to reduce deficits present at admission, it is reasonable to evaluate what effect the supplement might have on the recovery of the child with edematous malnutrition. The low magnesium diet did not appear to limit recovery from edematous malnutrition. This level of magnesium intake was associated with significant reductions in muscle and serum magnesium concentrations persistent throughout recovery (Table 5). There was no clinical difference between these two dietary groups at recovery (Table 3). This indicates that magnesium supplementation is not essential for full clinical recovery from malnutrition. Several investigators (29–35) have reported the concurrence of muscle potassium depletion with magnesium deficiency. It is of interest to note that the supplementation of magnesium was associated with a recovery of muscle magnesium without alteration of muscle potassium concentrations while on the A period diet. This is evidence that magnesium deficiency plays little or no role in the genesis of muscle K depletion present in these children. We have previously reported (14) the fact that muscle capacity for potassium is reduced in edematous malnutrition and that potassium supplements are of no effect unless the primary nutritional deficiencies are treated. Magnesium, however, is at least partially repleted independently from nutritional recovery (Fig. 1). Complete recovery of muscle electrolyte composition is possible in the face of documented magnesium depletion (R period in the unsupplemented subjects) and magnesium repletion occurs independently of electrolyte recovery (A_3 period of the supplemented subjects). Nevertheless, magnesium supplementation may have an effect on the rate of recovery of muscle composition. In the supplemented subjects, muscle potassium concentrations were higher during early dietary periods T_1, T_2 ($P < 0.05$), and T_{3-4} indicating an earlier recovery of muscle composition of these subjects. The myofibrillar nitrogen to collagen nitrogen ratio increased in the T_{3-4} in the supplemented subjects. This increase, which reflects the cytoplasmic mass, did not occur until the T_5 period (2 weeks later) in the unsupplemented children. These studies of muscle composition indicate that magnesium may play a role in promoting recovery of muscle composition but that supplementary magnesium is not essential for recovery of normal muscle composition. The evidence is not conclusive, however, because of differences between the subjects in series I and II.

Conclusions

A combination of balance studies and tissue and serum magnesium analyses reveal that there is a deficit of magnesium present

from admission in the majority of children with edematous malnutrition. These further indicate that the continuing requirements can be met by a magnesium intake of one mEq/kg per day, however, deficits present at admission may require up to 2.7 mEq/kg per day by mouth. The supplementation of oral intake with parenteral magnesium administration is indicated in the presence of severe diarrhea because of the poor efficiency of absorption of magnesium.

Tissue and serum studies of magnesium concentration indicate that recovery of magnesium concentrations occur when adequate magnesium is supplied. Clinical recovery, however, was not dependent upon restoration of serum and muscle concentrations to normal. An apparent increase in rate of recovery of body weight, muscle mass as evidenced by creatinine excretion, and muscle composition was present in the supplemented subjects. This reflected a possible 7 to 10 day acceleration of the rate with which normal body composition was attained. It is impossible to determine conclusively whether this acceleration of recovery was due to the magnesium supplementation or whether it was a product of the slight but statistically significant difference in nutritional indices present at admission between the two groups. It can be concluded that magnesium depletions do not inhibit nutritional rehabilitation and that a retention of 0.66 mEq/kg per day of magnesium supplements was well tolerated and probably beneficial.

In a previous analysis of electrolyte, water and nitrogen requirements during nutritional rehabilitation, we recommended that a diet of whole cow's milk be used. To reduce the renal solute load and to increase potassium intake, we recommended that the milk be diluted, two parts to one part of a solution of 15% dextromaltose which contained 1.5% potassium chloride (21). This would provide for a reduced sodium intake while meeting the requirements for nitrogen and potassium. From the present study, we can recommend a further modification of the rehabilitation formula so that oral magnesium intake is in the range of 2.7 mEq/kg per day. This can be simply achieved by adding 0.5% $MgSO_4 \cdot 7\ H_2O$ to the diluting solution. If the diluted milk were taken at a minimal rate of 150 cc/kg/day (100 kcal/kg per day), this formula would meet the average ongoing and deficit requirements for magnesium present at admission. If oral intake of magnesium were inhibited by severe gastrointestinal or other intercurrent illness, the mean continuing losses could be met by the administration of 0.5 to 0.7 mEq of magnesium sulfate per kilogram per day by parenteral routes.

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