Vitamin D resistance in magnesium deficiency[1-3]

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ABSTRACT Four patients with gastrointestinal disorders, and one patient with chronic alcoholism presented with both hypocalcemia and hypomagnesemia. Pharmacological doses of either ergocalciferol or dihydrotachysterol did not correct the hypocalcemia except in one patient who had a minimal rise in serum calcium. Parathormone levels were high in three patients and exogenous parathormone given to the fourth subject failed to elicit a rise in serum calcium, implying impairment of the calcemic response to parathormone. Magnesium repletion simultaneously corrected the hypomagnesemia and hypocalcemia. Balance data suggested that the rise in serum calcium was in part, at least, due to increased mobilization of minerals from bone. While the mechanism remains speculative, it appears that magnesium facilitates the release of calcium from bone in the presence of adequate amounts of vitamin D and parathormone. *Am. J. Clin. Nutr.* 29: 854-858, 1976.

The term "vitamin D resistance" has been variously used in medical literature, but it has usually indicated the persistence of hypocalcemia when greater than 120,000 units of vitamin D_3 or 1.0 mg of dihydrotachysterol (DHT) is being administered daily. The latter figures are usually the upper limit of replacement therapy in uncomplicated hypoparathyroidism (1, 2). Some of the causes of resistance to physiological doses of vitamin D are now known to be related to abnormalities in vitamin D metabolism, e.g., biliary cirrhosis (3), renal insufficiency (3), and perhaps one form of vitamin D-dependent rickets (4). Another factor, namely magnesium depletion has recently been associated with resistance to vitamin D and the latter has been partially corrected, at least in certain patients with hypoparathyroidism (5-8) and rickets (9), when magnesium was given. We have encountered vitamin D_3 or dihydrotachysterol resistance in four patients of gastrointestinal disease and one case of chronic alcoholism, all of whom had hypomagnesemia and hypocalcemia. Studies have been carried out prior to and during magnesium repletion that suggest that resistance to the calcemic effect of vitamin D or its analog is ameliorated when magnesium is given.

Patients and methods

Pertinent clinical data on the five patients studied are presented in Table 1. With the exception of CR, the patients were known to us previously, and multiple determinations of serum Ca, Mg, and phosphorus (P) were done before any therapeutic manipulations. These determinations were repeated during vitamin D administration and during Mg repletion. The daily urinary excretion of these ions was similarly determined. PTH levels were measured in LV, GS, and AH before any therapy, and in CR after she had received vitamin D.

An Ellsworth-Howard test (10) was done on eight normal subjects and the hypomagnesemic patients, although in LV, MC, and CR this was done after they had received vitamin D. The results are expressed as changes in phosphorus clearances rather than changes in the quantity of P excreted per hour. AH was also given parathyroid extract (PTE) 200 units, intramuscularly every 6 hr for eight doses.

Therapeutic trials with oral DHT were carried out in three patients. Patients were given about three times the daily dose used for replacement therapy in hypoparathyroidism, that is GS received 3.75 mg daily for 7 days; AH, 2.5 mg daily for 10 days, and MC, 2.5 mg daily for 6

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weeks. LV and CR were given ergocalciferol by their family physicians. LV received 150,000 units orally each day for 6 weeks; and CR, 500,000 units intramuscularly two or three times per week for 3 months. Mg repletion was undertaken immediately after the therapeutic trial with vitamin D and was carried out on the Clinical Research Center under balance conditions, with constant dietary intake. The oral administration of 10 ml of an 8% mg $(OH)_2$ suspension three times daily supplied 82.5 mEq of elemental mg each day. Aliquots of duplicate diets and homogenized stool collections were digested with concentrated H_2SO_4, ashed, dissolved in 12 N HCl, and appropriately diluted for mineral analysis. Atomic absorption spectrophotometry was used to determine Ca (11) and Mg (12) in all samples. P was determined by the method of Fiske and Subbarow (13) adapted to an automated analysis. PTH level were determined by the radioimmunoassay by Dr. C. D. Hawker (14, 15) which utilizes bovine parathormone and recognizes antigenic determinants between residues 35 and 84 (the COOH-terminal). Serum levels of 25 OH cholecalciferol levels were done by one of the authors (TH) using the method previously described (16).

Results

The initial serum Ca, Mg, and P levels are presented in Table 2. All the patients had serum Mg levels below 1.2 mEq/liter, and the daily excretion was less than 2 mEq except for CR who was excreting 6 mEq (Fig. 1). CR, with sprue, received a gluten-free diet throughout the study, and chose a 3,000 calorie diet, with 45 mEq of Mg. She might well have corrected her Mg depletion on this diet alone over a long time, since Mg balance was positive prior to supplementation. The normal serum Mg levels in our laboratory

TABLE 1
Patients' clinical data

Patient	Primary diagnosis	Age	Fecal fat	Serum			
				Albumin[a]	Alkaline phosphatase	PTH	25 OH C[b]
			g/day	*g%*	*IU*	*pg/ml*	*ng/ml*
AH	Intestinal bypass for obesity	47		2.3	122	232	13.2
CR	Gluten sensitive enteropathy	40	9.4	2.6	205	421	131
MC	Regional enteritis	18	2.2	1.9	101		
LV	Chronic alcoholism	41	2.7	3.5	232	506	180.0
GS	Regional enteritis	46	47.9	2.2	271	593	9.1
	Normal		<7.0	3.5-5.0	<87	255 ± 46	10-30

[a] No change in serum protein levels occurred during the experimental period. [b] 25 OH cholecalciferol.

TABLE 2
Serum Ca, Mg, and P before therapy, during vitamin D therapy and Mg repletion

	Patients				
	AH	CR	MC	LV	GS
Serum Ca (mg/100 ml)					
Control[a]	5.3 ± .08[b]		7.2 ± .26	8.3 ± .09	5.2 ± .14
Vitamin D[a]	7.0 ± .08[c]	6.1 ± .07	7.4 ± .08	7.9 ± .17	5.1 ± .08
Mg repletion[a]	8.0 ± .08[c]	7.4 ± .14[c]	8.1 ± .08[c]	9.2 ± .17[c]	8.3 ± .11[c]
Serum Mg (mEq/liter)					
Control	0.97 ± .03		1.15 ± .06	0.85 ± .02	0.54 ± .01
Vitamin D	1.02 ± .02	1.07 ± .04	1.27 ± .02	0.86 ± .01	0.54 ± .02
Mg repletion	1.45 ± .03[c]	1.50 ± .14[d]	1.65 ± .05[c]	1.42 ± .02[c]	1.58 ± .03[c]
Serum P (mg/100 ml)					
Control	3.6 ± .14		3.9 ± .22	3.9 ± .20[c]	2.5 ± .04
Vitamin D	3.6 ± .12	4.5 ± .22	3.7 ± .07	2.5 ± .20	2.9 ± .31
Mg repletion	3.0 ± .09[c]	4.3 ± .17	4.3 ± .14[c]	4.6 ± .07[c]	3.1 ± .10

[a] Control data include 4 to 6 serum values prior to therapy and 3 to 6 values were obtained during vitamin D treatment. Data during magnesium repletion are from the last 6 values of the repletion period, with the exception of LV where the observation period was short. Data used here for calculating means occasionally fell outside the time span of Figure 1. [b] All data are mean ± SEM. [c] $P < 0.01$. [d] $P < 0.02$, all other values have $P > 0.1$.

range from 1.5 to 2.1 mEq/liter. The patients were all hypocalcemic (our normal range is 8.5 to 10.5 mg/100 ml) even when considered in relation to their reduced serum protein levels (17) (Table 1). The serum P levels were within normal limits.

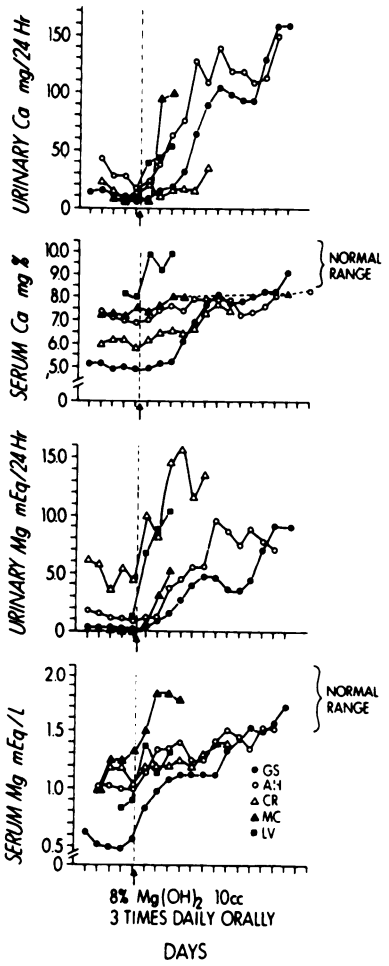

FIG. 1. Effect of Mg repletion on serum and urinary Ca, Mg, and P.

Four of the five patients had PTH levels determined (Table 1). Three had high levels appropriate for their low serum calcium values. The fourth, AH, who had a PTH level within normal range, but low for his serum calcium, was given 200 units of parathormone intramuscularly every 6 hr for eight doses. He did not show any significant rise in serum Ca, which was 5.4 mg/100 ml initially and 5.8 mg/100 ml at the end of the procedure.

The phosphaturic responses of the hypomagnesemic patients and a group of normal subjects to intravenous PTE are presented in Table 3. LV and GS who had remarkably low phosphorus clearances, as well as MC, increased their clearances at least 2-fold. AH and CR who responded minimally to PTE, however, had relatively higher phosphorus clearances to begin with. Two of our normal subjects had abnormally high base-line phosphorus clearances, which may have been related to calcium infusions given 36 hr prior to the test period. Nevertheless, their phosphaturic response to PTE was normal.

The effects of vitamin D administration on serum Ca, Mg, and P are presented in Table 2. Vitamin D administration was ineffective in raising serum Ca and Mg except in AH who showed a 1.7 mg/100 ml rise in serum Ca. Serum P was likewise unaffected by vitamin D except in LV who had an unexplained drop in her serum P. Twenty-five OH cholecalciferol levels were done on four of the five subjects (see Table 1) after the administration of vitamin D or DHT. LV and CR had a definite abundance of 25 OH vitamin D in their sera. The normal values for AH and GS are explained by the fact that assay

TABLE 3
Phosphorus clearances of hypomagnesemic patients and eight normal subjects before and after PTE, 200 units, intravenously

Patient	Control C_P[a]	Maximal C_P after PTE	% of Control
	ml/min	*ml/min*	
AH	27.5	31.5	115
CR	13.6	18.2	134
MC	6.0	16.1	268
LV	1.8	11.8	656
GS	1.1	3.4	309
Normal	4.6–26.5	13.6–44.8	168–473
	(12.8 ± 7.9)[b]	(28.7 ± 12.8)[b]	(257 ± 103)[b]

[a] Mean of 2 or more clearance periods. [b] Mean ± SD.

measures only 25 OH D_3, not 25 OH DHT. However, with their normal 25 OH cholecalciferol, it seems reasonable to assume that, with the supplement of DHT given, they would have had supranormal levels of 25 OH DHT as well.

Supplementation with Mg, however, produced a significant rise not only of serum Mg but of serum Ca as well (Table 2). Twenty-four hr excretions of these ions increased in concert with the rise of the serum levels (Fig. 1). Balance data showed no consistent trend of change in calcium and phosphorus balance when magnesium supplementation was given. Magnesium retention as a result of the supplement, however, was incontrovertible.

Discussion

Impaired synthesis or release of PTH has been shown to be present in patients with primary hypomagnesia (18, 19). Altered responsiveness to PTH has been suggested in other patients with magnesium deficiency (20, 21). In three of the five patients presented here appropriately high levels of circulating parathormone in relation to their serum calcium values were present. Subject AH probably had a subnormal level for his serum calcium, but failed to show a rise in serum calcium with exogenous parathormone. The phosphorus clearances were markedly low in GS and LV implying some resistance to endogenous PTH. Intravenous administration of PTE, however, did increase the phosphorus clearances normally in three of the five patients. It would appear that the phosphaturic response to endogenous PTH or exogenous PTE in hypomagnesemic patients is variable, and the renal unresponsiveness is relative rather than absolute. Our data also suggest a deficient calcemic response to PTH. It is perhaps pertinent that the calcemic response to PTH is highly dependent upon vitamin D while the phosphaturic response is less dependent, if at all (22).

Administration of pharmacological doses of vitamin D or DHT had no effect on serum Ca in our patients. Significant vitamin D absorption has been demonstrated in steatorrhea (23), tropical sprue (24), and nontropical sprue (25), and the normal or elevated 25 OH cholecalciferol found in these subjects rules out malabsorption of vitamin D as a factor. The data would suggest that pharmacological doses of vitamin D have little calcemic effect in Mg deficiency.

Mg repletion invariably resulted in a rise of serum Ca in the patients. Conceivably increased intestinal absorption of calcium could have contributed to the correction of the hypocalcemia. A high Mg intake has been reported to result in more positive Ca balance despite an increase in urinary excretion (26, 27). Our data are not sufficient to rule this possibility in or out. However, the rapidity of the rise in serum calcium (2 to 3 days) might indicate an alternate mechanism, namely increased bone resorption (28).

Mobilization of bone minerals to maintain Ca homeostasis can only be achieved by PTH or pharmacological doses of vitamin D in vivo. PTH mediated bone resorption, however, requires the presence of adequate amounts of vitamin D and Ca ions (29). Raisz et al. (30) have further shown in bone culture studies that a critical amount of Mg is necessary for PTH-mediated bone resorption to proceed optimally. It is not known whether a critical amount of Mg at a local site is also required for bone resorption mediated by pharmacological doses of vitamin D in the absence of PTH. Recent developments have revealed that the major effect of vitamin D is not due to the parent vitamin but rather to its more active hydroxylated metabolites. Whether the hydroxylation step that occurs in the kidneys (3) requires an adequate amount of Mg is also not known. In any event, the patients with Mg deficiency previously reported (6, 8, 9) and the patients reported here did not respond normally to pharmacological doses of vitamin D or vitamin D analog. All these data would suggest that adequate amounts of magnesium are required for the optimal expression of pharmacological vitamin D action and parathormone on bone mineral release.

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