Hypomagnesemia with Increased Metabolism of Parathyroid Hormone and Reduced Responsiveness to Calcitropic Hormones

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A patient with severe hypomagnesemia due to chronic alcoholism is presented who repeatedly exhibited marked hypocalcemia with a dissociation between radioimmunoassay findings for mid region of parathyroid hormone (PTH-M) and immunoradiometric assay findings of serum intact PTH (PTH-intact). Serum PTH-M was moderately elevated whereas serum PTH-intact was in a low normal range every time when her serum magnesium (Mg) concentration was markedly reduced. There was also a marked reduction in serum osteocalcin concentration. Supplementation of Mg resulted in a sharp increase in serum PTH level with a rapid disappearance of the dissociation between the two immunoassays of PTH. Shortly after serum PTH and $1,25(\text{OH})_2\text{D}$ levels reached their peak, serum osteocalcin started to increase, and was elevated into a supranormal level with normalization of serum Ca concentration. Mg is thought to act as a mimic/antagonist of calcium (Ca), and high extracellular Ca is shown to cause an inhibition of secretion with a stimulation of degradation of PTH. Thus, these observations are consistent with the hypothesis that Mg deficiency causes an increase in the metabolism of PTH and a reduction in the secretion of bioactive intact PTH by increasing the sensitivity of parathyroid cells to Ca. In addition, the fact that hypocalcemia disappeared concomitant with a marked increase of serum osteocalcin from undetectable levels suggest that refractoriness of bone to calcitropic hormones is present which plays a significant role in the development of hypocalcemia under hypomagnesemia, and that serum osteocalcin can be a good marker for the assessment of the responsiveness of bone to calcitropic hormones in these patients.

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Introduction

Magnesium (Mg) deficiency has been shown to cause functional hypoparathyroidism with hypocalcemia (1). Previous studies demonstrated that serum parathyroid hormone (PTH) concentration is suppressed in patients with hypomagnesemia (2, 3). In addition, there has been data to suggest that the responsiveness of adenylate cyclase to PTH is also impaired by Mg deficiency, and refractoriness to PTH has been postulated (4–6). However, the exact mechanism of functional hypoparathyroidism in Mg deficiency is as yet unclear partly because

of a lack of reliable clinical markers for the assessment of parathyroid function and bone turnover.

Recently, sensitive assays of serum PTH concentration have been developed. Midregion PTH assay (PTH-M) is a radioimmunoassay using sequence-specific antibodies against midportion of PTH. Because the antibodies recognize inactive carboxyl fragments as well as intact PTH, a major portion of measured PTH-M is inactive fragments which are much more abundant in the serum (7, 8). Another is an immunoradiometric assay using antibodies against amino- and carboxy-terminal portion of PTH, which detects only intact molecule of PTH

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(PTH-intact) (9). As a marker for the clinical assessment of bone turnover, the measurement of serum osteocalcin concentration has become a useful tool (10, 11). In the present study, these parameters were simultaneously measured to assess the secretion and metabolism of PTH as well as responsiveness of bone to PTH in a patient who repeatedly exhibited hypocalcemia due to hypomagnesemia.

Materials and Methods

Serum and urinary Ca and Mg levels were measured by an autoanalyzer (Hitachi model 705 and 736, Tokyo, Japan). Serum PTH-M was determined with a kit using an antibody against human PTH(44–68) (Yamasa Shoyu Co., Choshi, Japan) (12). The detection limit of the assay was 50 ng/l, and intra- and inter-assay coefficient of variance (CV) were 4.6% and 8.6%, respectively. Serum PTH-intact was measured by two-site immunoradiometric assay using anti-human PTH(1–34) and anti-human PTH(39–84) goat antibody (Nichols Institute, CA) (9). Anti-human PTH(39–84) antibody was immobilized onto polystyrene beads, and anti-human PTH(1–34) was radiolabeled with ^{125}I . Synthetic human PTH(1–84) was used as a standard. The detection limit of the assay was less than 5 ng/l, and intra- and inter-assay CV's were 5.8% and 6.0%, respectively. Serum osteocalcin was determined by a radioimmunoassay using anti-osteocalcin rabbit antiserum (CIS Inc., France) (11). Detection limit of the assay was 0.25 mg/l, and intra- and inter-assay CV's were less than 10%. Serum 25-hydroxyvitamin D [25(OH)D] was measured by competitive protein assay using vitamin D-deficient rat serum, and serum 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$) by radioreceptor assay using Yamasa $1,25(\text{OH})_2\text{D}_3$ receptor (Yamasa Shoyu Co., Choshi, Japan) as reported previously (13).

Case Report

A 53-year-old woman was repeatedly admitted to our hospital because of severe diarrhea and appetite loss. The patient had a long history of alcohol intake, and alcoholic liver dysfunction had been noted. Five months

before the first admission, diarrhea and appetite loss developed after a large amount of alcoholic ingestion. She kept drinking thereafter, and was admitted to our hospital. She appeared to start drinking soon after the first discharge, and was readmitted to our hospital with similar symptoms two months after discharge.

Her parathyroid function and parameters of Ca and Mg metabolism at the initial examination of each admission are listed in Table 1. A marked hypocalcemia and hypomagnesemia were observed with normal renal function. In the face of hypomagnesemia, fractional excretion of Mg was not suppressed as reported previously (13). In addition, serum PTH-M level was moderately elevated whereas PTH-intact concentration was in the low normal range despite the presence of hypocalcemia on both occasions.

As shown in Fig. 1, restriction of alcohol along with refeeding without any artificial Mg supplementation resulted in a sharp increase in serum PTH-M and PTH-intact levels with disappearance of the dissociation between these two measurements. However, despite the marked increase in both PTH-M and PTH-intact levels on the 5th hospital day, hypocalcemia persisted. Serum Ca was normalized on the 10th day when serum PTH levels were also normalized. These data suggested that there was a refractoriness to PTH under these circumstances, and that disappearance of the refractoriness caused a normalization of both serum Ca and PTH levels.

In order to test the possibility of refractoriness to PTH at the kidney and bone under hypomagnesemia, serum level of $1,25(\text{OH})_2\text{D}$ and osteocalcin were simultaneously followed at the second admission. As shown in Fig. 2, serum $1,25(\text{OH})_2\text{D}$ level was normal on admission, whereas serum osteocalcin concentration was markedly reduced despite the normal serum $1,25(\text{OH})_2\text{D}$ concentration. Serum 25(OH)D concentration was normal (27 nmol/l). The patient was again followed with the ingestion of regular meal without any artificial supplementation of Mg. Six days after admission, there was only a slight increase in serum Ca and Mg levels. However, as observed at the first admission, both PTH-M and PTH-intact started to increase, and the dissociation between them disappeared. Serum creatinine concentration and glomerular filtration rate were unchanged

Table 1. Serum Levels of Ca, Mg, Creatinine, PTH-M and PTH-intact at First and Second Admissions

	Serum Ca (mmol/l)	Serum Pi (mmol/l)	Serum Mg (mmol/l)	FE_{Mg} (%)	Serum Cr ($\mu\text{mol/l}$)	PTH-M (ng/l)	PTH-intact (ng/l)
First admission	1.97	1.52	0.41	5.2	90	760	36
Second admission	1.47	1.13	0.41	4.8	90	910	21
Normal	2.20	0.80	0.70	3.5	50	180	13
range	–2.56	–1.60	–1.20	–7.0	–110	–560	–53

Fig. 1. Clinical course of parathyroid function and parameters of Ca and Mg metabolism at the first admission. After admission, alcohol intake was discontinued, and the patient was given a regular meal without any artificial supplementation. The shaded areas represent normal ranges.

throughout the second admission, and serum BUN was even lower at the admission ($4.6 \mu\text{mol/l}$) compared to that on the 6th hospital day ($6.8 \mu\text{mol/l}$). Serum PTH levels reached their peak on the 10th day when $1,25(\text{OH})_2\text{D}$ also rose sharply to a maximal level of 219 pmol/l . These observations were in contrast with those of Rude et al (14) in hypomagnesemic patients showing reduced serum $1,25(\text{OH})_2\text{D}$ concentrations which may remain low one to two weeks after Mg administration, and suggested that the kidney responded normally to PTH in enhancing the production of $1,25(\text{OH})_2\text{D}$ in this patient. Although PTH and $1,25(\text{OH})_2\text{D}$ were above the upper limit, serum Ca was still low and osteocalcin was undetectable. Serum Ca and osteocalcin gradually increased and were normalized on the 14th day of admission, when PTH and $1,25(\text{OH})_2\text{D}$ fell into near normal range. Four weeks after admission, serum Mg concentration rose to 0.66 mmol/l and all the other parameters became normalized except that serum osteocalcin was elevated to far beyond the normal range.

Discussion

PTH secretion is known to be affected by extracellular Mg. *In vitro* studies have demonstrated that high extracellular Mg reduces and low extracellular Mg enhances PTH secretion from parathyroid cells (14). In contrast, not only an elevation (15) but also a reduction in serum

Fig. 2. Clinical course of serum Ca, Mg, PTH-M, PTH-intact, $1,25(\text{OH})_2\text{D}$ and osteocalcin concentration at the second admission. The patient was followed with refeeding without any artificial Mg supplementation as in Fig. 1. The shaded areas represent normal ranges.

Mg concentration suppresses serum PTH levels in humans (16, 17), and impaired secretion of PTH has been thought to be one of the major mechanisms of the development of hypocalcemia in Mg deficiency. However, in most of those previous clinical studies, the reliability of radioimmunoassays was controversial due to the poor sensitivity and specificity of the antibodies used (18). In the present study, two sensitive assays of PTH (PTH-M recognizes inactive midregion and PTH-intact detects only bioactive intact molecule of PTH) were simultaneously performed in a patient who repeatedly exhibited hypomagnesemia. It was found that serum PTH-intact was in a low normal range which was inappropriately low for the reduced serum Ca concentration, whereas the serum PTH-M concentration was moderately elevated on two independent occasions with marked hypomagnesemia. Consistent with these observation, Allgrove et al (19) reported that there is a dissociation between serum PTH concentrations using amino-terminal (PTH-N) and carboxy-terminal (PTH-C) specific antibodies, and that PTH-C is elevated in all patients with hypomagnesemia whereas PTH-N is reduced in patients with marked hypomagnesemia. The present observations confirmed those previous results by using much more

sensitive immunoassays, and demonstrated that the serum levels of bioactive intact PTH decrease and the proportion of inactive carboxyl fragments increase under hypomagnesemia. A similar dissociation between serum PTH-M and PTH-intact concentration has been noted in hypercalcemic patients with primary hyperparathyroidism (18). In those patients, the elevation in serum PTH-M is more pronounced than the PTH-intact concentration, and PTH-M is thought to be a better clinical tool for the diagnosis of primary hyperparathyroidism (18). Thus, in both of these circumstances, there is a possibility that the proportions of inactive carboxyl fragments increases because of an enhanced metabolism of PTH. Although the dissociation between PTH-M and PTH-intact is also commonly observed by an impairment in renal function, the serum creatinine concentration in this patient did not alter throughout the course, and the BUN/creatinine ratio was even lower at the admission when there was a dissociation between serum PTH-M and PTH-intact concentration.

Elevation in the serum Ca concentration has been shown to inhibit the synthesis and stimulate the metabolism of PTH in parathyroid cells (20–22). Increasing evidence favors the view that these effects of extracellular Ca are mediated through the interaction with a putative plasma membrane “Ca receptor”, which provokes an increase in intracellular Ca concentration through transmembrane signal transduction system (23) to cause an inhibition of PTH secretion (24). High serum Ca concentration is also shown to accelerate the hepatic and renal degradation of PTH (25). Mg appears to compete with Ca for these Ca receptors causing a rise in intracellular Ca concentration, but much higher concentration of Mg are necessary to induce a similar response (23). Thus, Mg may act as a mimic/antagonist of Ca (26). In fact, Mahaffee et al (27) reported an *in vitro* study using rat parathyroid cells showing that deletion of Mg from the medium caused a reduction in PTH release at a constant Ca concentration, and that PTH secretion was enhanced by increasing the Mg concentration up to 2 mM with a constant Ca level in the medium. These results are in good agreement with the present clinical observations, and are consistent with the assumption that hypomagnesemia reduces the competitive inhibition by Mg of the binding of Ca to its receptors, and that parathyroid and possibly other cells may respond to serum Ca with much higher sensitivity under hypomagnesemia. As a result, a reduction in PTH secretion associated with an enhancement of PTH degradation in the face of normal or even low serum Ca ensues by hypomagnesemia.

Another proposed mechanism for the development of hypocalcemia in Mg deficiency is a refractoriness of target tissues to PTH (4). It has been reported that the response of cyclic AMP to PTH is reduced in kidney and bone by Mg deficiency (3, 5, 6). In addition, a decrease

in extracellular Mg concentration causes an impairment of the skeletal response to PTH and $1,25(\text{OH})_2\text{D}_3$ in organ cultures of fetal rat long bones (28). Graber and Schulman (29) reported that serum Ca did not increase despite the administration of $1,25(\text{OH})_2\text{D}_3$ unless Mg was supplemented in a hypomagnesemic patient with postsurgical hypoparathyroidism. However, none of the previous clinical studies have presented convincing evidence to suggest that the skeletal response to calcitropic hormones is in fact impaired in patients with hypomagnesemia. In the present patient, the serum osteocalcin concentration was below the detection limit during Mg deficiency, and remained low even when serum PTH and $1,25(\text{OH})_2\text{D}_3$ were markedly elevated. Because osteocalcin is present exclusively in bone and has been shown to closely reflect bone turnover (30), these results support the previous assumption that the responsiveness of bone to calcitropic hormones is suppressed by hypomagnesemia. In addition, the fact that serum Ca concentration normalized after the elevation of serum osteocalcin to a supranormal level suggests that the refractoriness of bone to these hormones plays a significant role in the development of hypocalcemia in patients with Mg deficiency.

In conclusion, the present study demonstrates that there was a dissociation between serum PTH-M and PTH-intact concentration in a patient with hypomagnesemia, and that supplementation of Mg resulted in a rapid disappearance of the dissociation between these two measurements with a sharp increase in their serum concentration. These results are consistent with the hypothesis that Mg deficiency causes an increase in the degradation of PTH and a reduction in the secretion of bioactive intact PTH by increasing the sensitivity of parathyroid cells to Ca. In addition, the fact that hypocalcemia disappeared concomitant with a marked increase in serum osteocalcin concentration after Mg supplementation from undetectable levels suggests that the refractoriness of bone to calcitropic hormones is present under hypomagnesemia, and that the serum osteocalcin concentration can be a good marker for the assessment of the responsiveness of bone to these hormones in patients with hypomagnesemic hypocalcemia.

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