A Case of Magnesium Deficiency Associated with Insufficient Parathyroid Hormone Action and Severe Osteoporosis

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Abstract. The relationship between osteoporosis and magnesium (Mg) deficiency is still controversial. Here we report a case of an 82-year-old woman with a giant adenomatous goiter and severe osteoporosis with multiple vertebral fractures, whose clinical course indicated that her osteoporosis was probably due to Mg deficiency. She visited our hospital for treatments of tetany. Laboratory data showed the existence of hypomagnesemia, hypocalcemia, hypokalemia, vitamin D deficiency, and slightly elevated intact PTH. Intravenous administration of Mg not only improved these electrolyte abnormalities but also increased serum levels of intact PTH, bone formation markers, 1,25-dihydroxyvitamin D, as well as bone resorption markers in the urine, and lowered urinary phosphate reabsorption. Hypomagnesemia on admission seemed to arise from long-lasting poor food intake and malnutrition, because it improved after the disappearance of dysphagia with a goiter resection. After the operation, BMD values at the lumbar spine and femoral neck obviously increased during 6 months of Mg supplementation without any specific therapies for osteoporosis. Mg deficiency in this case seemed to cause impaired secretion of PTH from the parathyroid and the refractoriness of bone and kidney to the hormone, which led to the suppression of both bone remodeling and renal vitamin D production. These processes were probably linked to her severe osteoporosis, which was reversed by Mg supplementation.

Key words: Magnesium, Hypomagnesemia, Osteoporosis, Parathyroid hormone, Adenomatous goiter

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SERUM calcium levels are normally regulated within a relatively narrow range by the parathyroid gland through a negative feedback mechanism: Increased secretion of parathyroid hormone (PTH) by a fall in blood calcium levels enhances the mobilization of calcium, mainly by bone resorption, and then calcium levels are rapidly restored. Chronic magnesium (Mg) deficiency would result in hypocalcemia [1, 2], because of the impairment of PTH secretion [3–7] and/or resistance of target organ to PTH action [4, 6, 8]. Previous studies have demonstrated that serum PTH concentration was suppressed in patients with hypomagnesemia [4, 5], and Mg substitution therapy enhanced PTH secretion and reversed PTH target-organ

resistance, and thus serum calcium concentration returned to normal within several days [4, 7]. In addition, Mg deficiency could inhibit the synthesis of 1,25-dihydroxy vitamin D (1,25(OH)₂D) [9–11] as well as its action on bone [11]. Accumulating data have shown that a long-term Mg deficiency and resulting hypomagnesemia could cause osteoporosis and bone fractures through these dysfunctions of PTH and vitamin D action [12, 13–19]. However, other studies have shown no relationship between Mg deficiency and osteoporosis [20–22], and it still seems to be controversial whether or not Mg deficiency could cause osteoporosis. Here we report a patient with a giant adenomatous goiter and severe osteoporosis exhibiting hypomagnesemic hypocalcemia, whose osteoporosis was reversed by Mg supplementation with chronological improvements in bone mineral density (BMD), serum calcium, PTH, bone metabolic markers, and 1,25(OH)₂D. These findings suggest that osteoporosis in this case was probably linked to Mg deficiency.

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Case Report

The patient was an 82-year-old Japanese woman. She was pointed out with a goiter in 1980. The goiter enlarged gradually and caused dysphagia and poor food intake. She was referred to Shimane University Hospital in 2005 because of tetany. She had no history of smoking, drinking, or abnormal menopause.

On admission, physical findings revealed body height, 130 cm; body weight, 30 kg; blood pressure, 128/82 mmHg; pulse rate, 80 beats/min; and body temperature, 37.2°C. She presented an extremely giant thyroid tumor that was 10 × 6 cm in diameter. Lymph nodes were not palpable. There were no abnormal findings in lung, heart or abdomen. No edema was found in pretibia or foot. Neurological examination showed that patella tendon reflex and Achilles tendon reflex were attenuated. Trousseau and Chvostek signs were positive, suggesting the complication of tetany.

Laboratory data on admission are shown in Table 1. There were hypomagnesemia, hypocalcemia and hypokalemia with serum magnesium (Mg) 1.1 mg/dl, serum calcium (corrected by serum albumin) (cCa) 7.6 mg/dl, and serum potassium (K) 2.2 mEq/l. Fractional excretions of these minerals, however, were not suppressed. There was vitamin D deficiency or insufficiency with serum 25(OH)D 5.6 ng/ml and slightly elevated serum intact PTH (88.8 pg/ml). Low FT3 was noticed, but TSH and FT4 levels were normal. Lumbar spine X-ray indicated several vertebral compression fractures (Th11,12, and L1-4), and dual-energy X-ray absorptiometry revealed severe osteoporosis with lumbar BMD 0.328 g/cm² (T-score; -6.16 SD) and femoral neck BMD 0.179 g/cm² (T-score; -5.57 SD).

Mg tolerance test [23] was performed to examine whether or not hypocalcemia and hypokalemia were secondarily caused by hypomagnesemia. After Mg tolerance test by intravenous Mg administration (720 mg/12 hr), serum intact PTH level was markedly elevated to 328 pg/ml and serum levels of cCa and K were simultaneously improved (Fig. 1), showing that hypocalcemia, hypokalemia, and relative hypoparathyroidism were due to hypomagnesemia. In order to examine whether or not there was refractoriness of bone and kidney to PTH under hypomagnesemia, we followed chronological changes in serum bone formation markers [bone-specific alkaline phosphatase (BAP) and osteocalcin (OC)] and urinary bone resorption markers [type I collagen cross-linked N-telopeptide (uNTX)]

Table 1. Laboratory data on admission

Biochemistry	
TP	5.1 g/dl
Alb	2.2 g/dl
AST	30 IU/l
ALT	20 IU/l
ALP	257 IU/l
BUN	20.7 mg/dl
Crea	1.33 mg/dl
Na	140 mEq/l
K	2.2 mEq/l
Cl	96 mEq/l
cCa	7.6 mg/dl
Ca ²⁺	1.98 mEq/l
P	1.8 mg/dl
Mg	1.1 mg/dl
Urinary biochemistry	
24hCcr	23 ml/min
K	31 mEq/day
Ca	28.8 mg/day
%TRP	96%
Mg	15.3 mg/day
Fe _{Mg}	4.65%
Mg tolerance test	
Urine Mg excretion rate	2.07%
Bone metabolic marker	
BAP	21.8 U/l
OC	2.1 ng/ml
uNTX	45.0 nMBCE/mMCR
DPD	9.1 nM/mMCR
Endocrinology	
Intact PTH	88.8 pg/ml
PTHrp	<1.1 pmol/l
25(OH)D	5.6 ng/ml
1.25(OH) ₂ D	10.0 pg/ml
Calcitonin	39.8 pg/ml
TSH	2.92 μU/ml
FT ₃	1.0 ng/dl
FT ₄	1.4 ng/dl
Thyroglobulin	610 ng/ml
anti-TPO Ab	<0.3 U/ml
anti-TG Ab	<0.3 U/ml
TBII	5.2%
TsAb	129%

cCa: serum calcium concentration corrected with serum albumin level; %TRP: tubular reabsorption of phosphate; Fe_{Mg}: fractional excretion of Mg; BAP: bone alkaline phosphatase; OC: osteocalcin; uNTX: urinary type I collagen cross-linked N-telopeptide; DPD: Deoxypyridinolin; 25(OH)D: 25-hydroxyvitamin D; 1.25(OH)₂D: 1,25-dihydroxyvitamin D; anti-TPO Ab: anti-thyroid peroxidase antibody; anti-TG Ab: anti-thyroglobulin antibody; TBII: TSH binding inhibitory immunoglobulin; TsAb: thyroid stimulating antibody

*Normal range: Mg tolerance test: >70%; intact PTH: 11–54 pg/ml; PTHrp: <1.1 pmol/l; 25(OH)D: 7.6–29.1 ng/ml; 1.25(OH)₂D: 27.5–68.7 pg/ml; BAP: 13.0–33.9 U/l; OC: 2.5–13.0 ng/ml; uNTX: <40 nMBCE/mM-Cr; DPD: 2.8–7.6 nM/mMCR.

Fig. 1. Chronological changes in intact PTH, cCa, and K after Mg administration. Intact PTH level was markedly elevated and serum levels of cCa and K were improved spontaneously and simultaneously after intravenous Mg administration (720 mg/12 hr).

and deoxypyridinoline (uDPD)], as well as tubular reabsorption of phosphate (%TRP), and serum $1,25(\text{OH})_2\text{D}$. When Mg was administered, we observed an temporal and prompt increase in serum intact PTH with concomitant decrease in %TRP and increase in $1,25(\text{OH})_2\text{D}$. Both bone formation and resorption markers were also increased. These results suggest that bone turnover and PTH resistance in bone and kidney were associated with Mg deficiency. These findings indicated that Mg was essential for PTH secretion from the parathyroid as well as PTH actions on the target organs, bone and kidney. Tetany also disappeared by Mg supplementation.

After normalization of Mg level under parenteral nutrition, the patient underwent the resection of thyroid tumor in the right lobe, and noticed the disappearance of dysphagia and the recovery of food intake. The resected specimen showed that the thyroid gland epithelium consisting of rich eosinophilic granular cells was arranged in cords and follicles. These cells did not have polymorphism and atypism and did not invade into blood vessels, suggesting that these finding were compatible with an adenomatous goiter. Her general condition improved after the operation, and serum levels of Mg and other minerals remained normal without any supplementation. Her postoperative thyroid function maintained normal by administration of levothy-

roxine. On six months with no supplement of Mg after the operation, her body weight was increased to 31 kg. BMD values at the lumbar spine and femoral neck were obviously increased to 0.383 g/cm^2 (T-score; -5.66 SD) and 0.212 g/cm^2 (T-score; -5.28 SD) with no specific medication for osteoporosis, respectively.

Discussion

The association between hypomagnesemia and hypocalcemia has been reported by several investigators. Impaired secretion of PTH caused by reduction in serum Mg levels has been thought to be one of the major mechanisms by which hypocalcemia develops in Mg deficiency [3–7]. PTH secretion is known to be affected by extracellular Mg *in vitro* [24] and *in vivo* [25, 26]. Quitterer *et al.* have revealed that PTH secretion was blocked independently of the extracellular Ca^{2+} concentration in primary human parathyroid cells, when Mg was decreased [27]. They suggested that the paradoxical block of PTH release under Mg deficiency was mediated through a novel mechanism involving an increase in the activity of $\text{G}\alpha$ subunits of heterotrimeric G-proteins [27], which is a key molecule in Ca-bone metabolism [28]. In our patient, intact PTH level was markedly increased by Mg administration, although it

Fig. 2. Chronological changes in bone markers, %TRP, and serum 1,25(OH)₂D after Mg administration. Bone metabolic markers (BAP, OC, uNTX, and DPD) were obviously raised, %TRP decreased and serum 1,25(OH)₂D level increased. These findings suggest that Mg administration improved the refractoriness of bone and kidney to PTH.

was already slightly high on admission. This observation suggested that her PTH secretion on admission was not sufficient enough to counteract hypocalcemia.

Another mechanism by which hypocalcemia develops in Mg deficiency is through the resistance of PTH actions on target organs such as bone [29] and kidney [29–31]. In our case, bone metabolic markers and 1,25(OH)₂D were not elevated and %TRP was not suppressed despite the high value of intact PTH on admission, suggesting that bone and kidney were refractory to PTH action. Moreover, bone metabolic markers apparently increased and %TRP decreased after the intravenous supplementation of Mg, showing that the administration of Mg improved not only PTH secretion from the parathyroid but also the refractoriness of bone and kidney to PTH.

Serum phosphate in this case was very low on admission despite the high normal level of %TRP. Mg deficiency is often caused by malnutrition, such as chronic alcoholism [1, 8, 31, 32] and gastrointestinal

disorders [1, 33, 34], which might also cause hypophosphatemia in our patient. Indeed, the complication of low T3 syndrome and vitamin D deficiency or insufficiency suggests the existence of malnutrition in this case. In addition, vitamin D deficiency or insufficiency might aggravate hypophosphatemia further.

Mg depletion is thought to impair vitamin D metabolism, because serum 1,25(OH)₂D concentrations are frequently low in patients with Mg deficiency [35], and Mg administration ameliorates the level of 1,25(OH)₂D in Mg-deficient patients [7]. It has been reported that the synthesis of 1,25(OH)₂D required a free intracellular magnesium concentration *in vitro* [36], and that Mg deficiency decreased the synthesis of 1,25(OH)₂D in kidney. Mg deficiency also inhibits the binding of PTH to bone tissue *in vivo* [11]. Thus, hypomagnesemia could deteriorate hypocalcemia via the impairments of vitamin D metabolism and PTH action. The clinical observation in our patient seems to accord well with this pathogenesis.

Mg content in bone, which is a storehouse of Mg, is thought to decrease under a condition of long-term Mg deficiency, thereby leading to impaired bone metabolism [13]. In addition, previous reports have shown that bone quality deteriorates under a low Mg condition [14, 15], and that subjects at low serum Mg levels are at risk for bone fractures [12]. It has been reported that dietary Mg supplementation affected bone metabolism and dynamic strength of bone in ovariectomized rats [16]. Family members affected with primary hypomagnesemia due to renal Mg wasting inherited in an autosomal dominant manner have been reported to demonstrate significant reductions in serum and lymphocyte Mg concentrations as well as decreased BMD values at the lumbar spine and proximal femur [17]. Taken together, these findings suggest that Mg deficiency might also act as a risk factor for osteoporosis [18, 19]. However, other studies have failed to find the association between Mg deficiency and osteoporosis [20–22], and there are still controversies about this issue. In this case, Mg supplementation elevated bone turnover, which helped her BMD increase, and increased in 1,25(OH)₂D level with relieving PTH resistance in bone and kidney.

Hypomagnesemia is known to arise from various disorders. Inadequate intake of Mg is one of gastrointestinal causes for hypomagnesemia. Our patient suffered from dysphagia because of her extremely giant thyroid tumor. Her nutritional status was improved

and serum Mg levels returned to normal after the resection of thyroid tumor with modest oral supplementation of Mg. Thus, we suspected that poor food intake persisting until the operation might have caused Mg deficiency and hypomagnesemia in this case. Not only Mg deficiency but also improvement in nutritional conditions by increased food intake after the operation seemed to contribute to her BMD increase. Elevations in serum IGF-I and 25(OH)D levels may participate in this process, although these hormone levels were not

measured again after the operation.

In conclusion, we presented a case of magnesium deficiency associated with insufficient parathyroid hormone action and severe osteoporosis. Severe osteoporosis might be caused by suppressed bone turnover and impaired activation of vitamin D due to the refractoriness of bone and kidney to PTH, as well as poor nutritional status caused by reduced food intake due to dysphagia related to the giant thyroid tumor.

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