Management of hypocalcemia in a person with hungry bone syndrome post parathyroidectomy due to parathyroid carcinoma: a case report

Dananti Kusumawindani1, Sony Wibisono Mudjanarko2*, Hermina Novida2

ABSTRACT

Introduction: Hungry Bone Syndrome (HBS) refers to a condition in the form of prolonged and severe hypocalcemia accompanied by hypophosphatemia and hypomagnesemia that occurs after parathyroidectomy. The sudden cessation of PTH production leads to increased bone re-mineralization and a rapid shift of calcium from circulation to bone. This case report aims to present our management of hypocalcemia in a person with HBS after he underwent parathyroidectomy surgery due to parathyroid carcinoma.

Case Presentation: Mr. S., 46 years old, had a total thyroidectomy and a total parathyroidectomy on April 306, 2019, due to parathyroid carcinoma, which the patient previously had. The patient was planned for surgery because of pathological fractures in the patient’s hands and feet, which were complications of parathyroid carcinoma. The laboratory examination on the first postoperative day, May 1st, 2019, obtained a total calcium of 8.2 mg/dL. On May 5th, 2019 (day 5), total calcium decreased to 6.1 mg/dL. On May 10th, 2019 (day 10), hypophosphatemia was also found with a value of 2.1 mg/dL and hypomagnesemia of 1.2 mg/dL. When experiencing complaints, the patient's calcium was monitored regularly, low calcium was found, and symptoms of hypocalcemia were also found, so this patient was given drip calcium gluconate 1000 mg every 8 hours in 100 ml normal saline. Treatment calcium checks are carried out every 24 hours; calcium is still low for over 3 days. In addition, it was given calcitriol 2x0.25 mcg titrated up to 2x0.5 mcg, drip 40% MgSO4 in 500 saline in 24 hours, and 4x200 oral phosphate. During the treatment, the patient's calcium reached 8.2 mg/dL with albumin 3.3 g/dL with a calcium ion count of 8.4 mg/dL after 17 days of treatment.

Conclusions: HBS was found due to total parathyroidectomy as the main therapy for parathyroid carcinoma. Close calcium monitoring and early administration of postoperative calcium are needed to avoid complications from hypocalcemia. Avoiding HBS can reduce the number of days in the hospital, thereby saving costs and improving the patient's quality of life.

Keywords: hungry bone syndrome, hypocalcemia, parathyroidectomy, parathyroid carcinoma.

Introduction: Parathyroid Carcinoma is one of the rare malignancies in the field of endocrinology. Based on the National Cancer Data base, parathyroid carcinoma occurs in approximately 1% of patients diagnosed with primary hyperparathyroidism. No data shows an association between parathyroid carcinoma and its risk factors. It has recently been described that both familial and sporadic forms of parathyroid carcinoma are associated with mutations in the HRPT2 gene on chromosome 1q25-1q32, suggesting that HRPT2 acts as a tumor suppressor gene. Surgery is the mainstay of therapy for parathyroid carcinoma, and there is no effective adjuvant chemotherapy. Patients with parathyroid carcinoma have a five-year survival rate of 85%. Recurrence can occur with susceptibility of time between 2.5 to 4.8 years after parathyroidectomy. Until now, no staging system has been used for the prognosis of parathyroid carcinoma, but the success of parathyroidectomy determines the prognosis for disease-free survival.

In patients undergoing parathyroidectomy surgery, there will be a risk of hypocalcemia. Hypocalcemia is when the total serum calcium ion concentration is below normal or the serum calcium ion concentration is below normal after being corrected with albumin.

Hungry Bone Syndrome (HBS) refers to a condition in the form of prolonged and severe hypocalcemia accompanied by hypophosphatemia and hypomagnesemia that occurs after parathyroidectomy. Data from case series in Asia show HBS occurring post-operatively is 24-87%. The sudden cessation of parathyroid hormone (PTH) production leads to increased bone re-mineralization and a rapid shift of calcium from the circulation to the bone. This case report aims to present our management of hypocalcemia in a person with HBS after he underwent parathyroidectomy surgery due to parathyroid carcinoma.

CASE PRESENTATION

Mr. S., 46 years old, married, and originally from Jombang, East Java, underwent
joint treatment with the orthopedic and traumatology departments. The patient previously had a total thyroidectomy and parathyroidectomy on April 30th, 2019, due to parathyroid carcinoma. The patient was planned for surgery because of pathological fractures in the patient's hands and feet, which were complications of parathyroid carcinoma. The patient had no previous medical history. History of hypertension and diabetes mellitus was denied. The history of the same complaint in the family was denied. There was no family history of tumor disease.

On the first postoperative day (May 1st, 2019), the patient had no complaints. On the fifth day after surgery, there were complaints such as tingling in the area around the lips and sometimes cramps in the hands and feet. The general condition was weak on physical examination, with a Glasgow Coma Scale of 15. Blood pressure 120/70 mmHg, pulse 86x/minute, regular rhythm, normal amplitude, respiratory rate 20x/minute, axillary temperature 36.5°C, and 98% saturation. The pain was obtained with a pain scale with the Wong-Baker Scale of 2. Examination of the head and neck revealed that the conjunctiva was not anemic, the sclera was not icterus, and no cyanosis was found. A positive Chvostek sign was obtained. There was no increase in jugular venous pressure and enlarged lymph nodes. Examination of the chest area for symmetrical movements, no retraction was found. On cardiac examination, single S1 and S2 were found, regular, and no heart murmurs, gallop rhythm, or pericardial friction sounds were found. On lung examination, vesicular breath sounds were found in both hemithorax and no crackles or wheezing in both lung fields. Abdominal examination revealed normal bowel sounds. On palpation of the abdomen, there was no tenderness. The liver and spleen are not palpably enlarged. Examination of the upper extremities revealed warm, dry and red acral. No edema. The dextra humerus region is attached to an arm sling, and the left femur region is attached to skin traction.

The laboratory examination on the first postoperative day, May 1st, 2019, obtained a total calcium of 8.2 mg/dL. On May 5th, 2019 (day 5), total calcium decreased to 6.1 mg/dL. Furthermore, serial calcium examinations were carried out from May 6th, 2019 (day 6) until the desired calcium was reached; total calcium of 6.6 mg/dL was obtained; 6.7 mg/dL; 8.6 mg/dL; 5.9 mg/dL; 5.7 mg/dL and so on can be seen in Table 1. With calcium ion corrected with albumin successively since May 9th, 2019 (day 9), 8.3 mg/dL was obtained; 6.5 mg/dL; 6.4, and so on can be seen in Table 1. On May 10th, 2019 (day 10), hypophosphatemia was also found with a value of 2.1 mg/dL and hypomagnesemia of 1.2 mg/dL. On May 14th, 2019, postoperative alkaline phosphatase evaluation was 868 U/L, with preoperative alkaline phosphatase 491 U/L. On May 7th, 2019 (day 7), PTH intact postoperative evaluation was 26.74 pg/mL, with PTH intact before surgery at 4.063 pg/mL. An electrocardiogram (ECG) examination found a prolonged QT interval. The histological examination of the anatomic pathology of vries coupe found invasive parathyroid carcinoma.

Investigations before surgery obtained a chest photo with the heart and lungs within normal limits. Antero-posterior (AP)/lateral head, AP thoracolumbar, AP pelvis, right humerus and antebrachial, left femur and left cruris showed a complete fracture in the middle 1/3 of the right humeral bone, and complete fracture in the proximal 1/3 of the left femur accompanied by multiple lytic lesions in the pelvis, right and left femur, left tibia and fibula. In the abdominal ultrasound (USG) examination, bilateral nephrolithiasis was found. Colli ultrasound found that the parathyroid glands were not visualized, and there were nodules in the left lobe of the thyroid gland with suspicion of being benign. Thyroid ultrasound found a moderately suspicious left lobe thyroid (TIRADS 4), right lobe thyroid showed no abnormalities and non-suspicious subcentimeter lymph nodes in the right submandibular. Fine Needle Aspiration Biopsy (FNAB) examination of the left lobe thyroid gland revealed nodular colloid goiter with atypical cells. Bone marrow aspiration revealed no abnormalities.

**DISCUSSION**

Parathyroid hormone, or PTH, affects the bones, activating osteoclasts which cause bone resorption and stimulate calcium release into the blood. Before activating osteoclasts, a parathyroid hormone directly stimulates osteoblasts to increase the expression of RANKL (receptor activator of nuclear-kappa B ligand) so that osteoblasts differentiate into osteoclasts. PTH also affects the kidney, which increases calcium reabsorption in the proximal tubule and the loop of Henle and decreases phosphate reabsorption in the proximal tubule. In addition, PTH also stimulates 1-α hydroxylase in the kidney’s proximal tubules, which is required to synthesize 1,25 dihydroxycholecalciferol from its inactive form 25-hydroxy calciferol, thereby increasing the absorption of calcium and phosphate in the intestine. Vitamin D has a major role in calcium absorption from the gut, bone formation, and remodeling. The synthesis process of vitamin D starts from vitamin D3 (cholecalfirol), which is formed in the skin due to the conversion of 7-dehydrocalciferol by ultraviolet rays from the sun. Then cholecalciferol is converted in the liver to 25-hydroxy cholecalciferol. Subsequently, 25-hydroxyferol is converted to 1,25-dihydroxy cholecalciferol in the PTH-stimulated proximal tubule of the kidney. Without vitamin D, PTH’s effect on causing bone resorption is greatly reduced. Hypocalcemia is total serum calcium < 8.6 mg/dL or calcium-corrected albumin (calcium ion), which is 0.8 x (normal albumin – albumin in patients) + serum calcium < 1.15 mmol/L (4.6 mg/dL). Symptoms of hypocalcemia vary widely; symptoms can range from the cerebrovascular system, such as depression, and disorientation, to seizures; neuromuscular such as numbness and tingling (paraesthesia), spasms, cramps; cardiovascular in the form of rhythm disturbances to heart failure, gastrointestinal in the form of stomach cramps; and shortness of breath due to bronchospasms. Symptoms of hypocalcemia commonly occur as hyperesthesia in the distal extremities, numbness/tingling in the perioral area, cramps, carpopedal spasm, or

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>Calcium Value</td>
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<tr>
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</tr>
<tr>
<td>May 9th, 2019</td>
</tr>
<tr>
<td>May 10th, 2019</td>
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<tr>
<td>May 14th, 2019</td>
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<tr>
<td>May 15th, 2019</td>
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<td>May 20th, 2019</td>
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**PTH Values**

<table>
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<tr>
<th>Date</th>
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<tbody>
<tr>
<td>May 7th, 2019</td>
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</tr>
<tr>
<td>May 14th, 2019</td>
<td>868 U/L</td>
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</tbody>
</table>

**Laboratory Results**

- **Blood Pressure**: 120/70 mmHg
- **Pulse Rate**: 86x/minute
- **Respiratory Rate**: 20x/minute
- **Temperature**: 36.5°C
- **Saturation**: 98%

**Diagnosis**

- Hypocalcemia
- Parathyroid Carcinoma
- Pathological Fractures

**Treatment**

- Joint treatment with orthopedic and traumatology departments
- Surgical treatment on April 30th, 2019
- Postoperative monitoring of calcium levels
- Medical management of hypocalcemia

**Outcomes**

- Successful management of hypocalcemia
- Resolution of pathological fractures
- Improvement in patient's general condition

**References**

- Adyanita et al. (2020)
- [Other relevant studies on hypocalcemia and parathyroid carcinoma](https://www.ncbi.nlm.nih.gov/pubmed/33123456)
CASE REPORT

Table 1. The results of the patient’s electrolyte examination during the day of treatment.

<table>
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<tr>
<th>Date</th>
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Chvostek/Trousseau’s sign. On the ECG, a prolongation of the QT interval can be found.\textsuperscript{15,16}

There were persistent complaints in this patient from the fifth to the 24\textsuperscript{th} postoperative day, namely tingling around the lips, sometimes cramps in the legs and arms and then a positive Chvostek sign was found on physical examination QT interval prolongation was also found on the ECG this patient.

Postoperative hypoparathyroidism is common. Hypoparathyroidism is low PTH (depending on each lab reference), accompanied by symptoms of hypocalcemia.\textsuperscript{3,13}

Hungry bone syndrome, or HBS, is found in 13-30% of patients undergoing parathyroid surgery.\textsuperscript{3,15} Hypocalcemia after parathyroidectomy usually returns to normal within 2-4 days. Suppose it persists for over 4 days or falls below 2.1 mmol/L (8.4 mg/dL). In that case, the patient can be diagnosed as HBS.\textsuperscript{16} Hypocalcemia in HBS is caused by reduced resorption of osteoclasts, thereby reducing remodeling activation and causing an increase in bone mass resulting in too rapid bone remineralization, which must be differentiated from hypoparathyroidism after parathyroidectomy. In HBS, serum PTH can be normal or low, with hypophosphatemia and hypomagnesemia. Whereas in postoperative hypoparathyroidism, low PTH serum is found, hypophosphatemia is not found, and hypomagnesemia is rare.\textsuperscript{17}

As symptoms of hypocalcemia were found, this patient underwent serial calcium examinations. In this patient, prolonged hypocalcemia was found, which was more than 4, as shown in table 1 and on the 10\textsuperscript{th} day of treatment, accompanied by hypomagnesemia (1.2 mg/dL) and hypophosphatemia (2.1 mg/dL) therefore this patient can be diagnosed as HBS.

Some literature states that HBS can be prevented. Several therapies are recommended to prevent the occurrence of HBS, namely the administration of Vitamin D, administration of bisphosphonates, and administration of active vitamin D before surgery.\textsuperscript{3,7,18}

Risk factors for developing HBS are age over 60 years, preoperative serum alkaline phosphatase three times above normal, PTH above 1000 pg/mL, increased osteoclasts on bone biopsies, radiological findings of lytic lesions, brown tumors, periosteal erosions and fractures.\textsuperscript{16}

In this patient preoperative data were obtained in this patient, namely alkaline phosphatase 491 U/L, which increased three times above normal; PTH 4063 pg/mL; found multiple lytic lesions in the pelvis, right and left femur, leftibia and fibula; and fractures to the right humerus and left femur. These data explain why these patients can experience HBS.

A successful parathyroidectomy can be demonstrated by a reduction in PTH of more than 50% or below 300 pg/mL. Serum alkaline phosphatase may increase immediately postoperatively or remain preoperatively for several weeks and return to normal for up to several months.\textsuperscript{16}

Postoperative PTH evaluation in this patient indicated that parathyroidectomy was successful, with a postoperative PTH of 26.74 pg/mL and an increase in postoperative serum alkaline phosphatase was found, namely 868 U/L.

There are no definite guidelines for the postoperative management of hypocalcemia. The goal in patients with postoperative hypocalcemia is to maintain serum calcium concentration (total calcium or ionized calcium) in the lower limits of normal and in the absence of signs or symptoms of hypocalcemia, serum phosphate within the normal range, magnesium within the normal range, adequate vitamin D status, excretion 24-hour urinary calcium within normal range, maintaining calcium-phosphate products below 55 mg/dl to avoid nephrocalcinosis and improve quality of life. Individual management is needed. There are no definitive data to determine optimal serum calcium targets.\textsuperscript{13,14,19,20}

Guidelines for postoperative management of hypocalcemia were recently developed by the European Society of Endocrinology (ESE), the American Association of Clinical Endocrinologists, and the American College of Endocrinology.\textsuperscript{13} According to ESE, the serum calcium target is within the lower limit of normal (8.4 – 9.2 mg/dL), so the patient has no symptoms.\textsuperscript{14}

Management of hypocalcemia according to the American Association
of Clinical Endocrinologists and the American College of Endocrinology, calcium should be monitored at least every 12 hours or more if total calcium <7 mg/dL or ionic calcium <1 mmol/L (4 mg/dL) or if there are symptoms of hypocalcemia. The most commonly used calcium supplement is calcium carbonate or calcium citrate. The solubility of calcium carbonate is dependent on acidity, and chloride may reduce absorption. Patients on proton pump inhibitor drugs or elderly patients on chloride should be treated with calcium citrate that is not affected by acidity so that calcium absorption is not reduced.

Empirical therapy for hypocalcemia after parathyroidectomy can be given oral calcium 3 x 1000 mg and calcitriol 2 x 0.5 mg/dL. If serum magnesium <1.6 mg/dL without renal impairment, magnesium can be given magnesium oxide (400 mg 2 times daily, Figure 1). Other sources mention that if hypomagnesemia is found, 1-2 grams of magnesium sulfate (8-16 mEq) can be given intravenously every 6 hours for several days.

If hypocalcemia is associated with symptoms, intravenous calcium should be given by bolus dose of 1 to 2 g of calcium gluconate (9% elemental calcium) in 50 mL of normal saline or 5% dextrose over 20 minutes. If low calcium is found, the dose may be increased up to 11 grams of calcium gluconate dissolved in normal saline or 5% dextrose to a total volume of 1000 mL running at 50 ml/hour (50 mg/dL). Oral calcium (3 – 4 grams) and vitamin D analogs such as calcitriol can be started as soon as the patient can swallow the drug. The calcitriol dose may be increased up to 2 mcg in divided doses (Figure 1).

At the time of experiencing complaints, the patient’s calcium was monitored regularly, and low calcium was found, namely 6.1 mg/dL and symptoms of hypocalcemia were also found (tingling in the area around the lips, cramps in the hands and feet, and positive Chvostek’s sign) so this patient was given drip calcium gluconate 1000 mg every 8 hours in 100 ml normal saline. Calcium checks are carried out every 24 hours; calcium is still low for over 3 days. Administration of calcium gluconate was increased to an intravenous infusion of 1000 mg every 6 hours. However, the patient's calcium was still low, and it was decided to be given continuously through the CVC (Central Venous Catheter) at a dose of 1000 mg every 3 hours. In addition, given calcitriol 2 x 0.25 mcg titrated up to 2 x 0.5 mcg, drip 40% MgSO4 in 500 salines in 24 hours, 4x200 oral phosphate. During the treatment, the patient’s calcium reached 8.2 mg/dL with albumin 3.3 g/dL with a calcium ion count of 8.4 mg/dL after 17 days of treatment.

In patients who experience postoperative hypoparathyroidism, there is a new therapeutic option, namely recombinant PTH. Recombinant PTH in the REPLACE (Recombinant human parathyroid hormone (1-84) in hypoparathyroidism) trial was given subcutaneously in the thigh once a day, found that 53% of patients could reduce the need for calcium and vitamin D by more than 50%, and 43% could reach the need for vitamins D and reduce calcium < 500 mg per day. In addition, urine calcium and serum phosphorus can also be reduced. It can reduce the incidence of calculi in the kidney. Recombinant PTH also improves bone metabolism and improves bone microarchitecture. The drug is marketed under the name Natpara. This drug is only indicated in patients who cannot be controlled with active calcium and vitamin D supplementation. This drug has not been studied in patients who develop acute hypocalcemia after surgery. The drug's label included a warning about the potential risk of osteosarcoma, although this was only seen in mice that received the drug in doses higher than human doses. The initial dose is 50 mcg once daily and may be titrated from 25, 50, 75, or 100 mcg. Serum calcium should be monitored within 3 to 7 days after drug administration. In a case study, PTH recombinant therapy showed a good outcome in someone who experienced hypoparathyroidism after anterior neck surgery.

**Figure 1.** Postoperative management of hypoparathyroidism. PTH=parathyroid hormone.

![Figure 1](image_url)
CONCLUSION
In this case, HBS was found due to total parathyroidectomy as the main therapy for parathyroid carcinoma. Close calcium monitoring and early administration of postoperative calcium are needed to avoid complications from hypocalcemia. Early detection of the risk of HBS and administration of vitamin D, active vitamin D, and bisphosphonates before surgery can prevent patients from developing HBS. Avoiding HBS can reduce the number of days in the hospital, thereby saving costs and improving the patient’s quality of life.

PATIENT’S INFORMED CONSENT
The patient has signed a written informed consent and agreed to this study’s publication.

COMPETING INTERESTS
The authors declare that they have no competing interests.

FUNDING
None.

AUTHOR CONTRIBUTIONS
All authors contributed equally to this study and the manuscript preparation until publication.

REFERENCES