Hungry Bone Syndrome: A Rare Complication Post Parathyroidectomy

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Abstract

Hungry bone syndrome (HBS), rarely named "bone starvation syndrome", severe hypocalcemia following parathyroidectomy (PTX) due to rapid drop of PTH after a previous long term elevated concentration and associated bone remineralisation, impairs the outcome of underlying parathyroid (PT) disease by affecting the quality of life, prolonged hospitalisation stay, and increased post-operatory re-admission rate. HBS prevalence widely varies according to studied population, 15–25% to 92% of patients diagnosed with renal hyperparathyroidism (RHPT), in cases with primary hyperparathyroidism (PHPT), might not be identified at all, but overall prevalence accounts for up to 15–20% of individuals with PHPT; generally, a more important risk of developing HBS is registered in participants with impaired renal function. Hypocalcemia (usually below the value of 8.2–8.4 mg/dL), a typically severe and even life-threatening unless prompt intervention, arises within the third (varying between the first/second and the fourth–seventh) post-operatory day and it usually progresses through a 3-day period of time up to 30 days, requiring intravenous calcium replacement. Associated hypophosphatemia, hypomagnesiemia, and, exceptionally, hyperkaliemia (in patients undergoing chronic dialysis) are identified. This severe, but transitory, event is followed by mild or asymptomatic hypocalcemia requiring oral calcium and vitamin D substitution, particularly calcitriol, which may take a few months up to a year in order to register the restauration of normal mineral metabolism without the help of any medication. Early after PT surgery, normal or high (but lower than pre-operatory level) parathyroid hormone (PTH) is essential for establishing HBS diagnostic since non-low PTH is the clue to differentiate the condition from post-surgery hypoparathyroidism (low PTH). Pre-operatory assessments that might be a clue for further developing HBS after Parathyroid surgery vary; the most common are extremely high serum PTH and bone formation marker alkaline phosphatase (AP), noting that HBS involves an increased osteoblastic activity in association with a normal or low osteoclastic activity. Correction of hypercalcemia and starting calcium replacement from the first day of PTx might improve the outcome of HBS.

Introduction

Hungry bone syndrome (HBS), severe hypocalcemia following parathyroidectomy (PTX) due to rapid drop of PTH (parathormone) after a previous long term elevated concentration in primary (PHPT) or renal hyperparathyroidism (RHPT), impairs the outcome of underlying parathyroid disease.Rapid, severe and persistent hyponatremia and its range of complications following parathyroidectomy (PTX) are referred to as postoperative hungry bone syndrome (HBS) in the literature.[1] HBS refers to patients with high bone turnover before surgery, but after surgery, the inhibition of osteoclast resorption by intact parathyroid hormone (iPTH) suddenly decreases, resulting in a sudden increase in the amount of calcium resorbed by the bone, and a rapid, severe and persistent hypocalcemia, which may be accompanied by hypophosphatemia and hypomagnesemia.[2] This occurs most frequently in patients with severe primary hyperparathyroidism (PHPT), secondary hyperparathyroidism, or tertiary hyperparathyroidism following PTX therapy. We report a case of HBS with the aim of illustrating the pathogenesis, pathophysiology, and perioperative treatment
strategies behind this type of disease.

Case Report

A 42-year-old female patient was admitted with complaints of abdominal pain since 1 week and accompanied by nausea and vomiting, poor diet and sleep.Blood chemistry on day 1 of admission: Serum

calcium 14.4 (8.5-10.1)mg/dl, ionic calcium 1.8 (1.12-1.32) mmol/dl, phosphorus 1.8 (2.5-4.9) mg/dl, total 25-hydroxy vitamin D 19.25 (30-100) ng/mL, PTH 709 (15-65) pg/mL. Ultrasonography of neck revealed Hypochoic lobulated lesion of approximately 20 x8x7.9 mm seen posteroinferior to lower pole of right lobe of thyroid favouring parathyroid adenoma, with clear boundaries, regular morphology and homogeneous internal echogenicity; color doppler flow imaging: striated blood flow signals were detected inside the nodule, and the origin of the parathyroid glands was considered. 99mTc-MIBI dual-phase imaging showed limited abnormal radioactivity in the lower pole of right lobe concluding parathyroid adenoma of lower pole of right lobe(fig 1). Preop usg guided marking was done(fig 2).

On day 5 since admission patient was posted for elective right lower pole parathyroid adenoma excision. under general anesthesia with endotracheal intubation and a 3 to 4 cm long curved incision was made along the dermatomal line of the neck in the low position, and the side of the lesion was explored according to the information of the preoperative image localization. The right inferior pole of the thyroid gland was fully exposed and lifted up, and the surrounding fat capsule and peritoneum were separated, and the recurrent laryngeal nerve was protected, and a clearly enlarged adenomatous lesion was seen in the right inferior parathyroid region. After complete resection of the lesion, the intraoperative PTH plasma levels (iPTH) decreased to

163 pg/mL, 35 pg/mL at 0 and 10 minutes, respectively, and the exploration of the remaining glands was terminated. The resected single gland was reddish-brown in color, rich in blood supply, about 20 x1 x1cm, and weighed about 7 g. Postoperative pathology was parathyroid adenoma(fig 3). On post op day one serum ionic calcium level was 1.4 mmol/L and serum total calcium was 10.3 mg/dl which were lower than the preop values. Patient was discharged with oral vitamin D3 and calcium supplements. On post op day 10 patient was readmitted with complaints of numbness in the face, hands and feet. Serum calcium level was found to be 9.2 mg/dl and ionic calcium was 1.16mmol/L. Patient was provided supportive treatment in form of oral vitamin D3 and calcium supplements and monitored for 3 days and after that patient was discharged on same supplements and being followed up regularly and patient currently is symptom free and in good health.

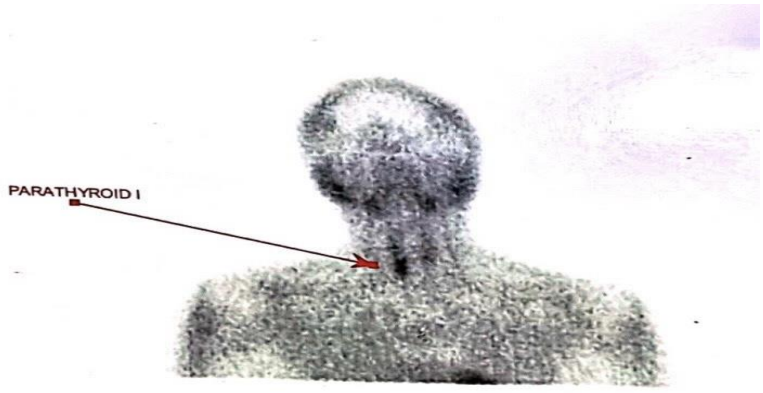
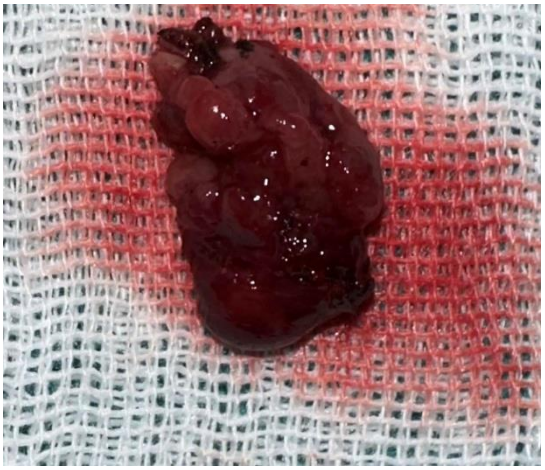
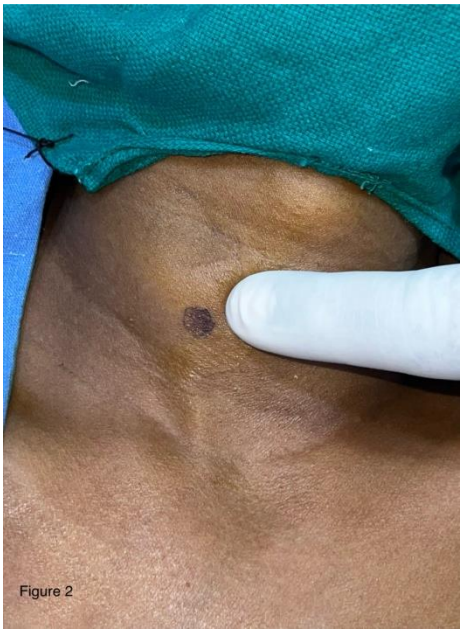
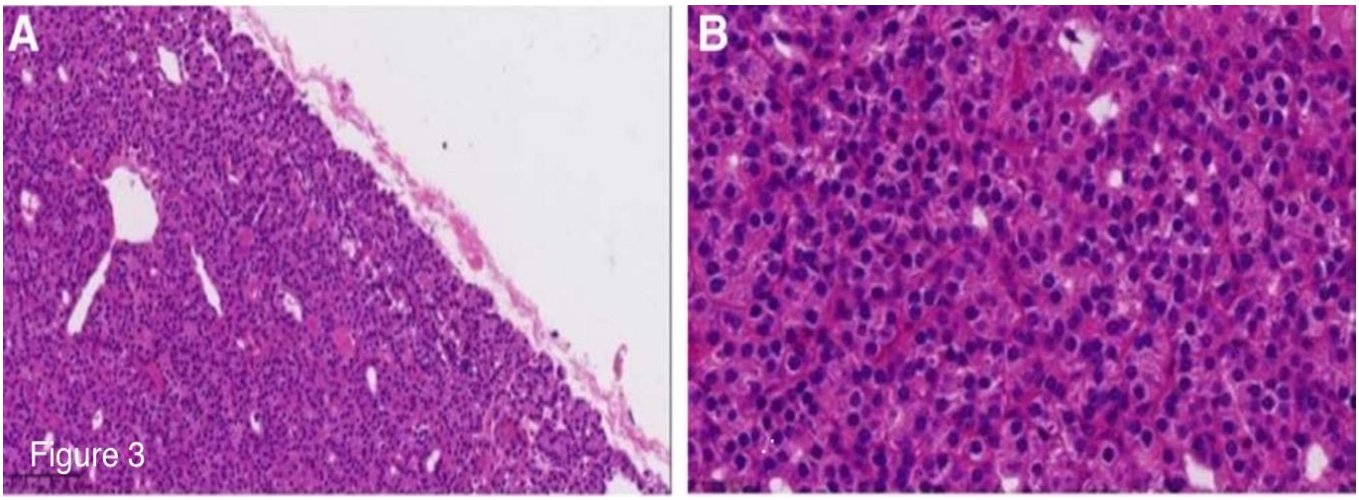


Figure 1







Discussion

The prevalence of PHPT is about 0.86%, most commonly seen in postmenopausal women, with a male-to-female incidence of 1:3 to 1:4.[1] Overproduction of PTH by 1 or more diseased parathyroid tissues leads to hypercalcemia, hypophosphatemia, kidney stones and increased bone resorption mainly in cortical bone.[2] PHPT includes asymptomatic, symptomatic and normocalcemic forms, and the guidelines for the treatment of asymptomatic PHPT are as follows serum calcium (above normal) of 1.0 mg/dL; creatinine clearance < 60 cc/min, 24-hour urinary calcium > 400 mg, high stone risk; T-score≤−2.5 (any location) on dual-energy X-ray bone densitometry bone density scanning at 3 sites (lumbar spine, total hip, femoral neck or distal 3rd of radius), fragility fracture, and vertebral compression fracture on spinal imaging.[3] Compression fracture,[3] symptomatic PHPT can involve multiple systems such as bone, kidney, gastrointestinal tract and nerves, etc. Intraoperative parathyroid hormone monitoring includes Vienna criterion, Halle criterion, Miami criterion, Rome criterion, and the commonly used "Vienna criterion." The "Vienna criterion" is a ≥50% decrease in iPTH within 10 minutes after resection from the pre-skinning "baseline."[4] The majority of PHPTs are monoadenomatous lesions (75–85%), followed by multiple lesions (hyperplasia in 10–15%; double adenomas in 2–12%) and carcinoma (1%).[5] HBS is defined as a condition of albumin-corrected serum calcium ≤2.1 mmol/L and normal or elevated serum whole iPTH levels, which develops on or after the 3rd postoperative day or persists for more than 3 days after surgery.

The prevalence is about 2.4% after PTX in PHPT patients with high bone turnover.[6] Fuller Albright was the first to describe PHPT patients with “stones, bones, and groans” in 1930, and the first to mention “HPT and groans” in a patient with PHPT, and was also the first to mention HBS.[7] In our case, the presence of serum calcium ≤2.1 mmol/L on the 3rd postoperative day and the persistent elevation of serum iPTH for more than 3 days were consistent with the diagnosis of postoperative HBS after PTX in a patient with symptomatic PHPT. Preoperative prediction of HBS risk factors is particularly important: (1) some scholars believe that preoperative PTH > 409 pg/mL can predict HBS[8]; (2) because menopausal women due to the reduction of estrogen accelerated bone loss, easy to combine with malnutrition, vitamin D deficiency, some scholars believe that postmenopausal women of advanced age is a predictor of HBS[9]; (3) removal of the parathyroid lesion volume or weight can be used as a predictor[10]; (4) the volume or weight of parathyroid lesions can be a predictive indicator[10]; (5) the volume or weight of parathyroid lesions can be a predictive indicator[10]; (6) the volume or weight of parathyroid lesions can be a predictive indicator.[10] In the study of Ko et al,[11] ALP mainly reflects bone resorption or destruction in bone metabolism, so preoperative ALP is a predictor of HBS, and preoperative increase in osteocalcin is also an independent risk factor; some scholars[12,13] believe that
serum 25-hydroxyvitamin D is sufficient, insufficient, deficient,and severely deficient in the following criteria: 30 to 100 ng/mL, 20 to 30 ng/mL, <20 to 20 ng/mL, and < 30 ng/mL, respectively; the criteria for adequate, inadequate, deficient, and severely deficient serum 25-hydroxyvitamin D are 30 to 100 ng/mL, 20 to 30 ng/mL, and < 20 to 90 ng/mL, respectively. 30 ng/mL, <20 ng/mL, <10 ng/mL, and severe preoperative vitamin D deficiency is a risk factor; Paepegaey et al[14] suggested that preoperative 18F-fluorocholine positron emission tomography/CT
suggestive of intense diffuse bone uptake may be a predictor of HBS in patients with PHPT. In addition bone mineral density, testosterone, 24 hours urinary calcium and albumin are also associated with HBS. There is often not enough awareness of HBS. The most common cause of postoperative hypocalcemia after PTX is impaired parathyroid blood supply characterized by low PTH, whereas HBS characterized by elevated PTH and increased bone formation is not so common. The sharp decrease of iPTH release after PTX, the sudden decrease of inhibition of osteoclast resorption, and the sudden decrease of osteoclast function broke the unstable equilibrium between large amount of bone calcium outflow and blood calcium inflow in the preoperative abnormally high osteoconversion pathophysiological state, and osteogenesis was greater than osteogenesis, and a large amount of blood calcium and phosphorus entered into the bone, and blood calcium and phosphorus of bone resorption were suddenly increased, and the
frequency of the activation of the new bone reconstruction sites was decreased, and the bone reconstruction intervals were activated. The frequency of new bone remodeling sites decreases, and the bone remodeling gap decreases, leading to a rapid, severe or even continuous decline in serum calcium, phosphorus and magnesium, manifesting electrolyte disorders such as secondary hypocalcemia, hypophosphatemia and hypomagnesemia.[15] Secondary hypocalcemia is associated with a secondary elevation of PTH, and hypophosphatemia is more common in postoperative patients with decreased bone resorption and
increased bone formation and normal urinary phosphorus excretion. Hypomagnesemia promotes refractory hypocalcemia by decreasing iPTH secretion and inducing iPTH resistance. This theory is supported by Liu et al[16] who found a rapid decrease in calcium and phosphorus levels and an increase in the number of mineralized nodules in cultures of osteoblast cell lines cultured in vitro at persistently high PTH concentrations. The short-term goal of HBS treatment is to replenish the circulating calcium deficiency and depleted skeletal calcium reserves, while the long term goal is to normalize osteoconversion and remineralization of bone, and to try to normalize osteoconversion with active cal-
cium supplementation postoperatively, and to try to recombine PTH, if necessary. The long-term goal is to normalize bone turn-over and bone remineralization, with aggressive postoperative calcium supplementation and, if necessary, recombinant PTH.[17] Hungry bone syndrome can also occur in other high bone conversion states after non-PTX, such as after total thyroidectomy for hyperthyroidism and in some patients with bone metastases from malignant tumors. In 2019, Kusuki and
Mizuno[18] reported a case of post-thyroidectomy HBS in a patient with Graves ’disease with severe thyrotoxicosis, elevated serum alkaline phosphatase, and low bone mineral density. Postoperatively, N-terminal prepeptide of pre-collagen type

1 increased significantly and anti-tartrate acid phosphatase 5b decreased indicating that post-thyroidectomy HBS persisted for 4 months. increase and decrease in anti-tartrate acid phosphatase 5b indicated that bone formation exceeded bone resorption after thyroid surgery and postoperative HBS lasted for 4 months. In 2018, Karunakaran et al[19] reported 39% incidence of HBS after total thyroidectomy in hyperthyroidism patients. In 2011, Huang et al[20] reported 2 cases of post-thyroid surgery HBS in hyperthyroidism patients, and suggested that thyroid hormone hyperactivation of osteoclast thyroid hormone receptor in hyperthyroidism was another uncommon cause of post-thyroid surgery HBS, and suggested that low magnesium in the post-thyroid surgery period should be the direct basis of diagnosis of HBS. In 2020 and 2018, there were case reports of HBS in patients with bone metastasis of prostate cancer and bone metastasis of gastric cancer.[21,22] In 1997, see[23] found that the incidence of hypocalcemia unrelated to hypothyroidism after subtotal thyroidectomy in patients with hyperthyroidism was 53%.

Conclusion

HBS may occur not only after parathyroid surgery, but also after thyroidectomy for hyperthyroidism and after other abrupt changes in pathophysiologic status of high bone conversion. Risk factors for the development of HBS include age, weight/
volume of parathyroid glands removed, imaging evidence of bone disease, and vitamin D deficiency. Therefore, it is important to pay close attention to ALP, iPTH, 24-hour urinary calcium, urinary creatinine, and the presence of vitamin D deficiency, as well as abnormalities in bone resorption and bone formation markers, and to aggressively supplement with calcium and vitamin D. The use of preoperative bisphosphonates and bone resorption antagonists mitigates the hyperosteoconversion. The pathophysiological state of high bone conversion can be alleviated by using bisphosphonates and bone resorption antagonists preoperatively, and the surgery can even be appropriately delayed if necessary; postoperatively, calcium supplementation should be actively used, and restructuring of PTH should be attempted if necessary, so as to restore bone conversion to normal, thereby reducing the incidence and severity of postoperative HBS.

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