Hungry bone syndrome: still a challenge in the post-operative management of primary hyperparathyroidism.

A systemic review of the literature

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Abstract

Hungry bone syndrome refers to the rapid, profound and prolonged hypocalcaemia associated with hypophosphataemia and hypomagnesaemia and exacerbated by suppressed parathyroid hormone levels, which follows parathyroidectomy in patients with severe primary hyperparathyroidism and preoperative high bone turnover. It is a relatively uncommon, but serious adverse effect of parathyroidectomy. We conducted a literature search of all available studies reporting a "hungry bone syndrome" in patients who had a parathyroidectomy for primary hyperparathyroidism, to identify patients at risk and address the pitfalls in their management. The severe hypocalcaemia is believed to be due to increased influx of calcium into bone, due to the sudden removal of the effect of high circulating levels of PTH on osteoclastic resorption, leading to a decrease in the activation frequency of new remodelling sites and to a decrease in remodelling space, although there is no good documentation for this. Various risk factors have been suggested for the development of a hungry bone syndrome, including older age, weight/volume of the resected parathyroid glands, radiological evidence of bone disease and vitamin D deficiency. The syndrome is reported in 25-90% of patients with radiological evidence of hyperparathyroid bone disease versus only 0-6% of patients without skeletal involvement. There is insufficient data-based evidence on the best means to treat, minimize or prevent this severe complication of parathyroidectomy. Treatment is aimed at replenishing the severe calcium deficit by using high doses of calcium supplemented by high doses of active metabolites of vitamin D. Adequate correction of magnesium deficiency and normalization of bone turnover are required for resolution of the hypocalcaemia which may last for a number of months after successful surgery. Pre-operative treatment with bisphosphonates has been suggested to reduce postoperative hypocalcaemia, but there are to date no prospective studies addressing this issue.
Introduction

Patients with primary hyperparathyroidism (PHPT) who undergo parathyroidectomy demonstrate a rapid decrease in serum calcium levels after successful removal of one or more hyperactive parathyroid gland(s). This decrease in serum calcium levels is usually mild and maximal 2 to 4 days post-operatively, independently of the size of hyperactive glands or pathological diagnosis (1-8). Persistence of hypocalcaemia for more than 4 days after parathyroidectomy may be due to intentional or accidental removal of all parathyroid glands, devascularization or trauma to residual parathyroid glands, but is also often due to long-term suppression of residual non-pathological parathyroid glands (1, 2, 8, 9).

The term “hungry bone” syndrome has been coined to the profound (serum calcium <2.1 mmol/l) and prolonged (longer than 4th day post-operatively) hypocalcaemia, which follows parathyroidectomy for severe hyperparathyroidism. This is usually associated with skeletal manifestations, reflected by pre-operative indices of high bone turnover, osteitis fibrosa cystica and/or "brown tumours". The severe hypocalcaemia is believed to be due to the greatly increased skeletal utilisation of calcium, thought to occur as a result of removal of the effect of high circulating PTH levels on bone with immediate arrest of bone resorption in the face of continuing and enhanced bone formation, although there is no good documentation for this.

Literature data on the hungry bone syndrome are scarce despite the still significant prevalence of this clinical problem and despite the challenges associated with its management. This has prompted us to perform a systemic review of the literature on this topic. To this effect, we performed a structured literature search in Medline, Embase and the Cochrane Library for studies reporting a "hungry bone syndrome" in patients who had undergone parathyroidectomy for primary hyperparathyroidism.

Methods

We searched PubMed, EMBASE, Cochrane Library, Web of Science, CINAHL and Science Direct, using the following search strategy: ("hypocalcaemia"[ti] OR "hypocalcemia"[MeSH Terms] OR "hypocalcemia"[ti] OR Hypocalcemic[ti] OR Hypocalcaemic[ti]) AND (hyperparathyroidism OR parathyroid adenoma OR parathyroid cancer OR "Parathyroid Neoplasms"[Mesh] OR parathyroidectomy OR hyperparathyroid* OR parathyroidectom* OR "Hyperparathyroidism/surgery" [Mesh]) AND (postoperative OR post-operative OR Postoperative Complications OR...
Postoperative Care OR pretreatment OR pre-treatment OR prevention OR preventive))
OR ("hungry bone" OR "hungry bones"). We restricted our search to publications in the
"English language" and on "Human subjects". We also checked the references of relevant articles for additional articles. Abstracts of meetings and unpublished results were not included in the study. The last search was performed on January 17, 2012.

Results

Systematic literature search

The initial search resulted in a total of 364 articles, 144 of which were excluded based on title and abstract, so that a total of 220 potentially relevant papers were retrieved for full assessment (Figure 1). Eligibility criteria included articles reporting a hungry bone syndrome after surgery for primary hyperparathyroidism in adult humans. Exclusion criteria were hypocalcaemia due to any other cause, non-complicated post-operative course, hungry bone syndrome in secondary or tertiary hyperparathyroidism and hungry bone syndrome in children. Comments or Letters to the Editor and articles only displaying a radiological picture were also excluded. One hundred and sixty nine of the 220 publications were excluded based on these exclusion criteria. Consequently, our search strategy ultimately resulted in 51 publications meeting the inclusion criteria of hungry bone syndrome after surgery for primary hyperparathyroidism in adult humans.

Pathophysiology of hungry bone syndrome

Bone remodelling consists of a series of cellular events on the bone surface, the function of which is to remove damaged bone through the process of osteoclastic bone resorption, and replacing it with new bone through the process of osteoblastic bone formation. The process of bone resorption which lasts about 2 weeks is followed by a reversal phase of 2-3 weeks duration, before new bone is formed, which lasts about 3 months. The remodeling space is the total amount of bone that at any time have been resorbed by osteoclasts but not yet reformed by osteoblasts during the coupled remodeling process because of the delay between resorption and formation. This space depends on the activation frequency of new remodeling sites, which is considerably increased in primary hyperparathyroidism, leading to mineral depletion of bone and significantly contributing to the hypercalcaemia of primary hyperparathyroidism (10-14).

In those patients with pre-operative high rates of bone turnover, successful parathyroidectomy curbs osteoclastic resorption, leading to a decrease in the activation
frequency of new remodelling sites and to a decrease in remodelling space leading to a consequent gain in bone mass. This is believed to be the cause of the rapid, profound and sometimes prolonged decrease in serum calcium, phosphate and magnesium levels. The duration of the hungry bone syndrome is defined as the duration of post-operative hypocalcaemia or time required for normalization of serum calcium following successful parathyroidectomy, which parallels normalisation of bone turnover and may last for up to 9 months, but exceptionally longer in cases of parathyroid carcinoma following radical excision of the tumour. In our experience, the duration of the hypocalcaemia is determined by the height of the increased bone turnover pre-operatively as well as by the time required for recovery of normal function of residual non-pathologic parathyroid tissue (unpublished personal observations).

Clinical manifestations of hungry bone syndrome
Severe hypocalcaemia (serum calcium concentration ≤ 2.1 mmol/l) is associated with neuromuscular irritability, clinically manifested by carpopedal spasms, perioral paresthesiae, tingling extremities, Chvostek sign and Trousseau sign (15-26). Patients can also develop generalized convulsions, which can ultimately lead to pathological fractures (27, 28), and ultimately if remaining uncorrected to coma and even death. Congestive heart failure, which is reversible after normalization of serum calcium concentration, has also been reported (15, 29).

Prevalence of hungry bone syndrome after parathyroidectomy
Data on the prevalence of hungry bone syndrome have been scarce and conflicting after original publications in the eighties of large case series suggesting that the syndrome develops post-operatively in up to 13% of patients with primary hyperparathyroidism (1, 3, 30). Recent case series from Asia reported much higher prevalence rates of 24-87% (31-34), whereas a case series from Saudi Arabia documented a prevalence rate of only 4% (35).

Risk factors for the development of a hungry bone syndrome
Age at time of surgery
Older age at time of surgery is a risk factor for hungry bone syndrome (1). Brasier et al. (1), showed that in a group of 198 patients with primary hyperparathyroidism, those who
developed hungry bone syndrome were 10 years older than patients with an uncomplicated post-operative course (61 ± 3 vs. 51 ± 1, \( P<0.05 \)).

**Laboratory investigations prior to surgery**

Patients who developed hungry bone syndrome had higher pre-operative levels of serum calcium, and almost 2-fold increased levels of PTH and of alkaline phosphatase compared to patients who had an uncomplicated post-operative course (Table 1) (1, 4, 36). However, Lee *et al.* (37) were not able to demonstrate a significant difference in pre-operative serum levels of calcium, PTH or alkaline phosphatase between 9 patients who developed hungry bone syndrome post-operatively and 14 patients who did not. Serum magnesium and albumin levels were found to be significantly decreased in patients who subsequently developed a hungry bone syndrome (Table 1) (1).

There were no available data on the predictive value of pre-operative bone markers other than alkaline phosphatase, such as procollagen type 1 amino-terminal propeptide (P1NP, a marker of bone formation) and beta-crosslaps (\( \beta \)-CTX, a marker of bone resorption). Depleted vitamin D status (low levels of 25(OH)D and 1,25(OH)\(_2\)D) has been suggested to be a risk factor for the development of hungry bone syndrome, by some, but not all, authors (1, 38, 39)

**Radiological bone disease prior to surgery**

Radiological evidence of PHPT-related bone disease has been reported to be an important risk factor for the development of hungry bone syndrome (4, 16, 17, 26, 27, 31, 40). Fourteen of 18 case reports on hungry bone syndrome indeed report skeletal abnormalities, such as subperiostal erosions, lytic lesions, brown tumours, and multiple fractures (15-19, 21-27, 29, 41-45). Osteitis fibrosa cystica was observed in 47-100% of patients who develop hungry bone syndrome (31, 36) and the syndrome was reported in 25-90% of patients with radiological evidence of PHPT-related bone disease compared to only 0-6% of patients without skeletal involvement (31, 39, 40).

**Volume and weight of resected pathological parathyroid gland(s)**

A large study in 198 patients with PHPT demonstrated that the volume and weight of the removed adenomas were significantly greater in patients who developed hungry bone syndrome compared to patients who had an uncomplicated post-operative course (5 ± 1 vs. 1 ± 0.2 cm\(^3\), \( P<0.05 \) and 4 ± 1 vs. 2 ± 0.2 gram, \( P<0.05 \), respectively) (1). Zamboni *et al.*
al. (46) confirmed this finding, by demonstrating that 11 of 16 patients with a single adenoma of > 2 gram developed transient post-operative hypocalcaemia versus only 3 of 21 patients with a single adenoma of <1 gram ($P < 0.001$).

There are no available data on the relationship between histological characterization of the resected pathological glands (adenoma vs. hyperplasia) and the development of hungry bone syndrome.

Biochemical changes associated with hungry bone syndrome

A rapid decrease in serum PTH levels to a mean of 1.7 ± 0.4 pmol/l follows successful parathyroidectomy in all cases of primary hyperparathyroidism (1). Serum calcium levels drop to levels <2.1 mmol/l within the first 3-4 days, but decrease further after the fourth postoperative day in patients with hungry bone syndrome (1). Serum phosphate levels decrease post-operatively and remain so for the duration of the syndrome (1, 17, 27, 31, 37, 38, 41, 47, 48). Hypomagnesaemia is frequently encountered (36). Serum alkaline phosphatase levels increase significantly post-operatively and remain elevated sometimes for up to 9 months after surgery (1, 17, 27, 31, 38, 40, 41, 43, 44, 49).

Agarwal et al. (31) also reported increased levels of osteocalcin, a marker of bone formation, and decreased urine crosslaps, a marker of bone resorption, in 51 patients one week after surgery, with serum osteocalcin levels normalising only 6 months after successful parathyroidectomy (31). In 3 of 51 patients with extreme osteopenia, bone turnover markers remained elevated for 1 year after successful parathyroidectomy (31).

Radiological changes associated with hungry bone syndrome

Removal of the excessive circulating levels of PTH shuts off bone-resorptive activity and leads to a rapid increase in bone mineral density. Case reports show an increase in bone mineral density of the lumbar spine of 17% at 10 weeks, 10% at 6 months and 27-65% at 1 year after parathyroidectomy (7, 44, 49, 50) and an increase in bone mineral density of the greater trochanter of 33% at 6 months and of 35-131% at 1 year after surgery (7, 50).

Bone mineral density increased post-operatively by a remarkable 332% within 1 year in Indian patients with overt skeletal disease and/or osteitis fibrosa cystica (31). Follow-up radiographs show recovery of subperiosteal resorption and remineralisation of "brown tumours", osteolytic lesions and fracture sites (7, 16, 27, 31). Skeletal scintigraphy shows an increased radioactive isotope uptake 1 month after parathyroidectomy, known as "flare phenomenon", which reflects a healing response due to a significant increase in bone
formation and consequent mineralization and high influx of calcium into the skeleton (16, 19). A moderately increased uptake can still be seen 8 months after parathyroidectomy (18) and a decrease in the number of lesions and a normalization of uptake in the remaining lesions one year after parathyroidectomy (16).

Management of hungry bone syndrome

The treatment of a hungry bone syndrome is aimed, in the short term, primarily at replenishing the depleted skeletal calcium stores. The first case reports of a hungry bone syndrome, which appeared in the late 70’s, described the difficulties encountered in the management of this severe complication of parathyroidectomy before active metabolites of vitamin D and their synthetic analogues became available for use in the clinic (15, 22, 26, 27). Persistence of severely decreased serum calcium levels of \( \leq 1.3 \) mmol/l were thus reported despite treatment with very high doses of calcium, magnesium and cholecalciferol (15, 26, 27). These management difficulties are, however, still being observed today, despite widespread availability of active vitamin D preparations (23).

The reported amount of calcium supplementation required to treat the severe hypocalcaemia varies between 6 and 12 grams per day (17, 21, 23, 29, 41, 44, 45). Initially, calcium is supplemented intravenously, but treatment with oral preparations should be initiated as early as possible, with concomitant use of adequate doses of active metabolites of vitamin D (calcitriol) or of alfacalcidol (2 to 4 ug per day) (17, 21-23, 38, 43-45), or very occasionally higher doses (unpublished personal observations), and with replenishment of magnesium stores as required. The amount of magnesium required to correct hypomagnesaemia has not always been reported, and supplementation has been variably given intravenously as magnesium chloride or sulphate or orally as magnesium sulphate (15, 17, 19, 22, 26, 38, 44). In 11 of 18 cases, serum magnesium level was not mentioned, and in 1 of 18 cases serum magnesium level was within the normal range (16, 18, 21, 23-25, 27, 29, 41-43, 45).

Treatment options to prevent hungry bone syndrome

Pre-operative treatment with vitamin D

Depleted vitamin D status has been postulated to be a risk factor for the development of hungry bone syndrome and it has generally been recommended to supplement vitamin D to normalize 25(OH) vitamin D levels, although there are so far no available data to
support the premise that this would contribute to the prevention or blunting of a hungry bone syndrome (1, 38).

Pre-operative treatment with bisphosphonates

Two case reports of patients with extensive hyperparathyroid bone disease, demonstrated that preoperative treatment with intravenous pamidronate given at a dose of 30 mg on 2 consecutive days or as a single infusion of 60 mg, resulted in a preoperative decrease in serum calcium and in a decrease (just 1500 mg calcium orally per day) or no post-operative calcium requirements (7, 51). One case report showed that a patient with a history of severe PHPT for longer than 8 years, who was treated with alendronate for 6 years, in addition to receiving a preoperative total dose of 180 mg pamidronate intravenously, did not develop a hungry bone syndrome post-operatively (52).

In a retrospective study, Lee et al. (37) also demonstrated that none of 6 patients who had received bisphosphonates pre-operatively (either oral clodronate 400-1600mg/day or intravenous pamidronate 60mg/day), developed hungry bone syndrome post-operatively, compared to 9 of 17 patients who had not been pre-operatively treated with bisphosphonates (Supplement Table 2). There were no significant difference in pre-operative mean serum calcium (3.00 ± 0.15 vs. 3.01 ± 0.04 mmol/l), PTH (34.8 ± 11 vs. 33.4 ± 10 pmol/l) or alkaline phosphatase (224 ± 50 vs. 174 ± 60 U/l) levels between groups. A retrospective case series of 46 patients with severe bone disease, who were treated with intravenous zoledronate pre-operatively also reported a low frequency of post-operative hungry bone syndrome of only 4% (35). Another retrospective case series of 6 patients with radiological features of osteitis fibrosa cystica, who were pre-operatively treated with bisphosphonates (oral alendronate 20-30mg/day for 4-6 weeks or a single dose of pamidronate 90 mg or ibandronate 150 mg intravenously) reported that none of the patients needed post-operative intravenous calcium supplementation (50).

In contrast, a case report of a patient with severe, prolonged and extensive bone involvement (florid radiological bone changes), has shown that a single dose of 60 mg intravenous pamidronate combined with calcitriol 1-2 ug/day was able to significantly decrease (but not normalize) serum alkaline phosphatase levels (1600 U/l to 420 U/l), but was not able to completely prevent a hungry bone syndrome (43). Four other case reports also show that treatment of severe hyperparathyroidism with alendronate (70 mg/week), pamidronate (twice 90 mg or 5 times 15 mg intravenously) or zoledronate (twice 4 mg
intravenously) was unable to completely prevent a hungry bone syndrome (23, 38, 44, 45) (Supplement Table 3).

Pre-operative treatment with active metabolites of vitamin D

Boyle et al. (53) showed that pre-operative treatment of severe hyperparathyroidism with 1,25(OH)\textsubscript{2}D (calcitriol) at a dose of 2 µg/day for 1-10 weeks significantly decreased pre-operative alkaline phosphatase levels in 3 of 7 patients with radiological bone cysts, and 3 other patients required little intravenous calcium supplementation to a total of less than 1 g in the first 12 post-operative days. In contrast, Heath et al. (4) showed that 6 patients with PHPT and radiological evidence of bone involvement, who were treated pre-operatively with 2 µg/day of 1,25(OH)\textsubscript{2}D for 1 week, were as likely to develop hungry bone disease as patients with PHPT and radiological evidence of bone involvement who did not receive active vitamin D preparations pre-operatively (2 of 6 vs. 1 of 6, respectively).

Discussion

Hungry bone syndrome is a relatively uncommon complication of parathyroidectomy for severe primary hyperparathyroidism associated with preoperative high bone turnover. It is characterized by a rapid, profound and persistent hypocalcaemia associated with hypophosphataemia, hypomagnesaemia and exacerbated by suppressed parathyroid hormone levels. The duration of the hungry bone syndrome is the time taken to remineralize the skeleton, which is also mirrored by normalization of bone turnover markers, by healing of radiological features of osteitis fibrosa cystica and brown tumours and by significant gains in bone mass.

A similar but less severe form of the syndrome may also be observed following medical or surgical treatment of hyperthyroidism associated with high bone turnover, in which hypocalcaemia may occur in up to 46% of patients (54) and last for up to 12 weeks after initiation of treatment. In contrast to the case with the HBS of severe primary hyperparathyroidism, in treated hyperthyroidism, hypocalcaemia is associated with appropriate significant increases in PTH levels (55, 56).

Our literature search suggests that the prevalence of hungry bone syndrome has decreased in the Western World over the last 2 decades, most likely due to the early detection of still asymptomatic primary hyperparathyroidism by routine calcium screening before the effects of high circulating levels of PTH on the skeleton, such as high bone turnover,
osteoporosis or osteitis fibrosa cystica become evident (38, 49), although exact numbers are missing.

One of the identified risk factors for a post-operative hungry bone syndrome is older age at the time of surgery. Older age being more often associated with vitamin D deficiency, a decrease in renal 1α-hydroxylase activity, and lower dietary calcium intakes (1), all 3 factors potentially contributing to a negative calcium balance and clinical bone disease (4). It has indeed been shown that patients with osteitis fibrosa cystica, have lower levels of 1,25(OH)₂D than expected, which may be due to high levels of serum calcium directly inhibiting renal 1α-hydroxylase production, or to hypercalcaemia-induced renal impairment with resulting further decreases in 1α-hydroxylase activity (57). A testable hypothesis for the development of bone disease, and for the development of a hungry bone syndrome, relates to the possibility that low circulating levels of 1,25(OH)₂D with resultant decreased fractional absorption of calcium, leads to undermineralization of the skeleton (1, 4). Low levels of 1,25(OH)₂D may thus represent a measurable risk factor for the development of a hungry bone syndrome, independently of age, although 25(OH)D deficiency has been proposed to be the more significant risk factor (38).

Pre-operative serum alkaline phosphatase levels reflect the state of bone turnover and, therefore, the degree of osteoclast activity and of bone resorption. It has been suggested that pre-operative serum alkaline phosphatase concentrations may predict the degree and duration of hypocalcaemia after successful parathyroidectomy (58). Other risk factors for the development of a hungry bone syndrome include evidence of bone disease, such as osteitis fibrosa cystica, subperiostal bone erosions or bone cysts (4, 15-17, 26, 27, 31, 40) and the volume and weight of the removed hyperactive parathyroid gland(s) (1, 3).

Treatment of the hungry bone syndrome is aimed in the short term primarily at replenishing the circulating calcium deficit, and in the longer term, at normalizing bone turnover and remineralising the skeleton. Doses of calcium and active vitamin D preparations required and duration of treatment are guided by serum calcium and bone turnover marker levels, aiming at normalization of bone turnover (3, 15, 20, 26-28, 49), which may sometimes last in excess of 12 months after successful surgery.

In the early stages of HBS, the doses of calcium supplements necessary to increase and maintain serum calcium concentrations within the normal range are too large to be tolerated orally, and intravenous administration is often required (15, 17, 21-23, 29, 41). When calcium-containing solutions are given intravenously, administration into large veins or via a central venous catheter is recommended to minimize the risk of local
irritation or tissue necrosis by accidental extravasation in surrounding tissues. Electrocardiographic monitoring is recommended as dysrhythmias may occur in case of too rapid correction of the hypocalcaemia (59). In prescribing oral calcium preparations, it is important to realize that different calcium preparations contain different amounts of elemental calcium. Of the available oral preparations, calcium carbonate has the highest % of elemental calcium (40%), followed by citrate salts (20%). Other calcium preparations are also available, although they do not contain sufficient elemental calcium per tablet and compliance may be affected by the large number of tablets required to be taken orally to achieve the same calcium level: calcium lactate (13%), calcium gluconate (9%) and calcium gluconate (6.6%) (20). If high doses of magnesium are required for the treatment of hypomagnesaemia, this should only be given intravenously in adequate dilutions of magnesium sulphate, and not intramuscularly or orally. Lower doses of magnesium can be supplemented as magnesium oxide orally, or magnesium sulphate intramuscularly. Hypocalcaemia does not resolve until the magnesium deficiency has been corrected. (3, 15, 26-28, 49).

Depleted vitamin D status has been postulated to be associated with an increased risk of developing postoperative hypocalcaemia and hungry bone syndrome (60-63). Preliminary data suggest that pre-operative correction of vitamin D deficiency may decrease levels of PTH and bone turnover, without exacerbating hypercalcaemia (60, 63, 64). Although the effect of preoperative vitamin D treatment on postoperative hypocalcaemia has not been evaluated by randomized controlled intervention studies in primary hyperparathyroidism, it is our experience that a preoperative replete vitamin D status is associated with a decreased likelihood of a severe or prolonged hungry bone syndrome (1, 38).

Bisphosphonates are antiresorptive agents, widely used in the management of osteoporosis and bone disorders associated with increased bone turnover, such as Paget's disease of bone or metastatic bone disease. In hyperparathyroid bone disease these agents inhibit osteoclastic bone resorption and decrease activation frequency of remodeling sites, thus resulting in refilling of remodeling space and increasing mineralization of bone (38, 65, 66). In this context preoperative bisphosphonate treatment would have a potential beneficial effect on the severity and duration of a hungry bone syndrome by significantly decreasing or normalising bone turnover before surgery is attempted (38, 67) In contrast, short-term preoperative treatment may exacerbate postoperative hypocalcaemia by just reducing bone resorption, without allowing time for a coupled decrease in bone formation. There are as yet no prospective studies or randomized control trials addressing
the use of bisphosphonates in the prevention or limitation of duration of a hungry bone syndrome. Data from case reports and small case series on the beneficial effect of preoperative treatment with bisphosphonates on the hungry bone syndrome in patients with hyperparathyroid bone disease (35, 37, 57, 67) or with longstanding severe PHPT (52) are conflicting (23, 27, 35-37). Some cases thus report failure of preoperative bisphosphonates to prevent HBS, although this was believed to be due to short duration of treatment or low dosage used, since serum alkaline phosphatase levels had not normalized before surgery (23, 38, 43-45).

Because low levels of 1,25(OH)$_2$D are a risk factor for the development of post-operative hungry bone syndrome (1, 39), it has also been hypothesized that pre-operative supplementation of 1,25(OH)$_2$D could shorten symptomatic hypocalcaemia and hospital course (1, 53, 57). Data on preoperative 1,25(OH)$_2$D supplementation in patients undergoing parathyroidectomy for severe primary hyperparathyroidism are also conflicting (4, 53). A major limitation of studies addressing the effect of bisphosphonates and/or active vitamin D preparations on the prevention of hungry bone syndrome, is the lack of patient randomization.

**Conclusion**

Hungry bone syndrome is a relatively uncommon, but serious complication of parathyroidectomy for primary hyperparathyroidism associated with high bone turnover. There are no clear guidelines for the management of the hungry bone syndrome but treatment is aimed at replenishing the severe calcium deficit and at restoring normal bone turnover with the use of high doses of calcium and active metabolites or analogues of vitamin D. Adequate correction of magnesium deficiency and normalization of bone turnover are required for resolution of the hypocalcaemia which may last for a number of months after successful surgery. Adequate pre-operative treatment with bisphosphonates may reduce the severity and duration of postoperative hypocalcaemia. Further prospective studies are needed to optimize pre- and postoperative treatment strategies in patients with primary hyperparathyroidism and skeletal manifestations, at high risk for a hungry bone syndrome.

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Table 1: Pre-operative laboratory data in patients with primary hyperparathyroidism who developed HBS following parathyroidectomy compared to those who did not.

<table>
<thead>
<tr>
<th>Laboratory investigation</th>
<th>Author</th>
<th>Patients who developed HBS</th>
<th>Patients who did not develop HBS</th>
<th>P-value</th>
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<tr>
<td>s-Calcium (mmol/l)</td>
<td>Brasier(^{(1)})</td>
<td>3.00 ± 0.05</td>
<td>2.88 ± 0.03</td>
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<td></td>
<td>Spiegel(^{(36)})</td>
<td>3.25 ± 0.05</td>
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<td>Heath(^{(39)})</td>
<td>3.94 ± 0.38</td>
<td>2.95 ± 0.15</td>
<td>&lt;0.01</td>
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<td>Lee(^{(37)})</td>
<td>3.00 ± 0.1</td>
<td>3.00 ± 0.08</td>
<td>0.7</td>
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<tr>
<td>s-PTH (pmol/l)</td>
<td>Brasier(^{(1)})</td>
<td>10.2 ± 2.00</td>
<td>5.7 ± 0.3</td>
<td>&lt;0.05</td>
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<td>Lee(^{(37)})</td>
<td>30.7 ± 10</td>
<td>32.9 ± 6</td>
<td>0.2</td>
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<tr>
<td>s-alkaline phosphatase (U/l)</td>
<td>Brasier(^{(1)})</td>
<td>68 ± 15</td>
<td>38 ± 2</td>
<td>&lt;0.05</td>
</tr>
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<td>Heath(^{(39)})</td>
<td>51 ± 37</td>
<td>12 ± 6</td>
<td>&lt;0.01</td>
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<tr>
<td></td>
<td>Lee(^{(37)})</td>
<td>248 ± 48</td>
<td>169 ± 31</td>
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<tr>
<td>s-magnesium (mEq/l)</td>
<td>Brasier(^{(1)})</td>
<td>1.5 ± 0.1</td>
<td>1.7 ± 0.04</td>
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<tr>
<td>s-albumin (g/dl)</td>
<td>Brasier(^{(1)})</td>
<td>3.9 ± 0.1</td>
<td>4.3 ± 0.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HBS: hungry bone syndrome, s: serum
Legend to the Figures

**Figure 1**: Flowchart of articles included in the systematic review.
Figure 1: Flowchart of articles included in the systematic review.

337 identified articles using search strategy

- 136 articles excluded on the basis of title and abstract
  - 70 articles based on patients with SHPT or THPT
  - 54 articles based on patients without hyperparathyroidism
  - 12 articles based on children

- 201 articles potentially relevant retrieved for more detail
  - 150 articles excluded on the basis of text
    - 158 articles based on PHPT patients but no hypocalcemia or hungry bone disease

45 articles included in the review

196x116mm (150 x 150 DPI)
Table 1: Pre-operative laboratory data in patients with primary hyperparathyroidism who developed HBS following parathyroidectomy compared to those who did not.

<table>
<thead>
<tr>
<th>Laboratory investigation</th>
<th>Author</th>
<th>Patients who developed HBS</th>
<th>Patients who did not develop HBS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>s-Calcium (mmol/l)</td>
<td>Brasier&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>3.00 ± 0.05</td>
<td>2.88 ± 0.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Spiegel&lt;sup&gt;(36)&lt;/sup&gt;</td>
<td>3.25 ± 0.05</td>
<td>3.00 ± 0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Heath&lt;sup&gt;(39)&lt;/sup&gt;</td>
<td>3.94 ± 0.38</td>
<td>2.95 ± 0.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Lee&lt;sup&gt;(37)&lt;/sup&gt;</td>
<td>3.00 ± 0.1</td>
<td>3.00 ± 0.08</td>
<td>0.7</td>
</tr>
<tr>
<td>s-PTH (pmol/l)</td>
<td>Brasier&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>10.2 ± 2.00</td>
<td>5.7 ± 0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Lee&lt;sup&gt;(37)&lt;/sup&gt;</td>
<td>30.7 ± 10</td>
<td>32.9 ± 6</td>
<td>0.2</td>
</tr>
<tr>
<td>s-alkaline phosphatase (U/l)</td>
<td>Brasier&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>68 ± 15</td>
<td>38 ± 2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Heath&lt;sup&gt;(39)&lt;/sup&gt;</td>
<td>51 ± 37</td>
<td>12 ± 6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Lee&lt;sup&gt;(37)&lt;/sup&gt;</td>
<td>248 ± 48</td>
<td>169 ± 31</td>
<td>0.1</td>
</tr>
<tr>
<td>s-magnesium (mEq/l)</td>
<td>Brasier&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>1.5 ± 0.1</td>
<td>1.7 ± 0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>s-albumin (g/dl)</td>
<td>Brasier&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>3.9 ± 0.1</td>
<td>4.3 ± 0.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HBS: hungry bone syndrome, s: serum