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

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Abstract

Hungry bone syndrome (HBS) refers to the rapid, profound, and prolonged hypocalcaemia associated with hypophosphataemia and hypomagnesaemia, and is exacerbated by suppressed parathyroid hormone (PTH) levels, which follows parathyroidectomy in patients with severe primary hyperparathyroidism (PHPT) 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 PHPT, 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 HBS, 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 vs only 0–6% of patients without skeletal involvement. There is insufficient data-based evidence on the best means to treat, minimise 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 normalisation of bone turnover are required for resolution of the hypocalcaemia which may last for a number of months after successful surgery. Preoperative treatment with bisphosphonates has been suggested to reduce post-operative hypocalcaemia, but there are to date no prospective studies addressing this issue.

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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 2–4 days post-operatively, and independent of the size of hyperactive glands or pathological diagnosis (1, 2, 3, 4, 5, 6, 7, 8). Persistence of hypocalcaemia for more than 4 days after parathyroidectomy may be due to intentional or accidental removal of all parathyroid glands, devascularisation 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' (HBS) 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 high preoperative indices of bone turnover, osteitis fibrosa cystica and/or 'brown tumours'. The severe hypocalcaemia is believed to be due to the greatly increased skeletal usage of calcium, thought to occur as a result of removal of the effect of high circulating parathyroid hormone (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 HBS 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 systematic 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 PHPT.

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 pretreatment 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 (Fig. 1). Eligibility criteria

included articles reporting HBS after surgery for PHPT in adult humans. Exclusion criteria were hypocalcaemia due to any other cause, non-complicated post-operative course, HBS in secondary or tertiary hyperparathyroidism and HBS 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 HBS after surgery for PHPT in adult humans.

Pathophysiology of HBS

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 remodelling space is the total amount of bone that at any time has been resorbed by osteoclasts but not yet reformed by osteoblasts during the coupled remodelling process because of the delay between resorption and formation. This space depends on the activation frequency of new remodelling sites, which is considerably increased in PHPT, leading to mineral depletion of bone and significantly contributing to the hypercalcaemia of PHPT (10, 11, 12, 13, 14).

In those patients with preoperative 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
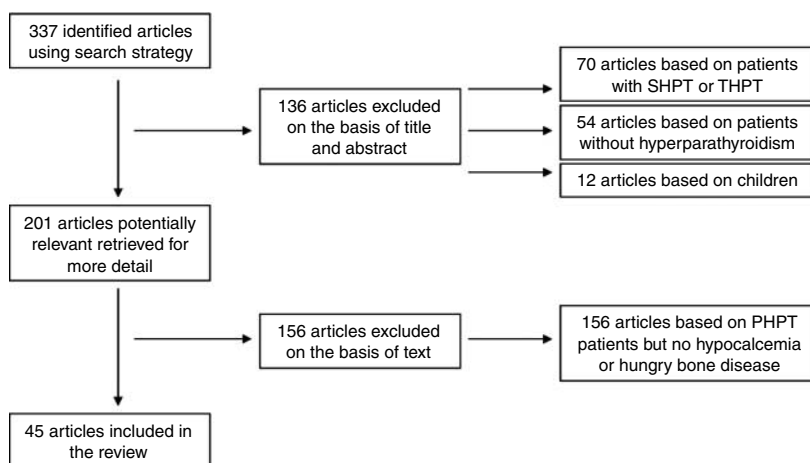
Figure 1 Flowchart of articles included in the systematic review. SHPT, Secondary hyperparathyroidism; THPT, Tertiary hyperparathyroidism; PHPT, Primary hyperparathyroidism.

serum calcium, phosphate and magnesium levels. The duration of the HBS is defined as the duration of post-operative hypocalcaemia or time required for normalisation 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 preoperatively as well as by the time required for recovery of normal function of residual non-pathologic parathyroid tissue (N A T Hamdy, 1990-2011, unpublished personal observations).

Clinical manifestations of HBS

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, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26). Patients can also develop generalised convulsions, which can lead to pathological fractures (27, 28), and ultimately if remaining uncorrected to coma and even death. Congestive heart failure, which is reversible after normalisation of serum calcium concentration, has also been reported (15, 29).

Prevalence of HBS after parathyroidectomy

Data on the prevalence of HBS have been scarce and conflicting after original publications in the 1980s of large case series suggesting that the syndrome develops post-operatively in up to 13% of patients with PHPT (1, 3, 30). Recent case series from Asia reported much higher prevalence rates of 24–87% (31, 32, 33, 34), whereas a case series from Saudi Arabia documented a prevalence rate of only 4% (35).

Risk factors for the development of HBS

Age at time of surgery Older age at time of surgery is a risk factor for HBS (1). Brasier & Nussbaum (1) showed that in a group of 198 patients with PHPT, those who developed HBS were 10 years older than patients with an uncomplicated post-operative course (61 ± 3 vs 51 ± 1, $P < 0.05$).

Laboratory investigations before surgery Patients who developed HBS had higher preoperative levels of serum calcium, and almost two-fold increased levels of PTH and alkaline phosphatase compared with 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 nine patients who developed HBS post-operatively and 14 patients who did not. Serum magnesium and albumin levels were found to be significantly decreased in patients who subsequently developed HBS (Table 1) (1).

There were no available data on the predictive value of preoperative bone markers other than alkaline phosphatase, such as procollagen type 1 amino-terminal propeptide (P1NP, a marker of bone formation) and β-crosslaps (β-CTX, a marker of bone resorption). Depleted vitamin D status (low levels of 25(OH)D and $1,25(OH)_2D$) has been suggested to be a risk factor for the development of HBS by some, but not all, authors (1, 4, 38).

Radiological bone disease before surgery Radiological evidence of PHPT-related bone disease has been reported to be an important risk factor for the development of HBS (4, 16, 17, 26, 27, 31, 39). Fourteen of 18 case reports on HBS indeed report skeletal abnormalities, such as subperiosteal erosions, lytic lesions, brown tumours and multiple fractures

Table 1 Preoperative laboratory data in patients with primary hyperparathyroidism who developed HBS following parathyroidectomy compared with those who did not.

Laboratory investigation	Authors	Patients who developed HBS	Patients who did not develop HBS	P value
s-Calcium (mmol/l)	Brasier & Nussbaum (1)	3.00 ± 0.05	2.88 ± 0.03	< 0.05
	Spiegel *et al.* (36)	3.25 ± 0.05	3.00 ± 0.03	< 0.001
	Heath *et al.* (4)	3.94 ± 0.38	2.95 ± 0.15	< 0.01
	Lee *et al.* (37)	3.00 ± 0.1	3.00 ± 0.08	0.7
s-PTH (pmol/l)	Brasier & Nussbaum (1)	10.2 ± 2.00	5.7 ± 0.3	< 0.05
	Lee *et al.* (37)	30.7 ± 10	32.9 ± 6	0.2
s-Alkaline phosphatase (U/l)	Brasier & Nussbaum (1)	68 ± 15	38 ± 2	< 0.05
	Heath *et al.* (4)	51 ± 37	12 ± 6	< 0.01
	Lee *et al.* (37)	248 ± 48	169 ± 31	0.1
s-Magnesium (mEq/l)	Brasier & Nussbaum (1)	1.5 ± 0.1	1.7 ± 0.04	< 0.001
s-Albumin (g/dl)	Brasier & Nussbaum (1)	3.9 ± 0.1	4.3 ± 0.04	< 0.001

HBS, hungry bone syndrome; s, serum.

(15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 29, 40, 41, 42, 43, 44). Osteitis fibrosa cystica was observed in 47–100% of patients who develop HBS (31, 36) and the syndrome was reported in 25–90% of patients with radiological evidence of PHPT-related bone disease compared with only 0–6% of patients without skeletal involvement (4, 31, 39).

Volume and weight of resected pathological parathyroid gland(s)

A large study on 198 patients with PHPT demonstrated that the volume and weight of the removed adenomas were significantly greater in patients who developed HBS compared with 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 g, $P < 0.05$ respectively) (1). Zamboni & Folse (3) confirmed this finding, by demonstrating that 11 of 16 patients with a single adenoma of > 2 g developed transient post-operative hypocalcaemia vs only three of 21 patients with a single adenoma of < 1 g ($P < 0.001$). There are no available data on the relationship between histological characteristics of the resected pathological glands (adenoma vs hyperplasia) and the development of HBS.

Biochemical changes associated with HBS

A rapid decrease in serum PTH levels to a mean of 1.7 ± 0.4 pmol/l follows successful parathyroidectomy in all cases of PHPT (1). Serum calcium levels drop to < 2.1 mmol/l within the first 3–4 days but decrease further after the fourth post-operative day in patients with HBS (1). Serum phosphate levels decrease post-operatively and remain so for the duration of the syndrome (1, 17, 27, 31, 37, 38, 40, 45, 46). 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, 39, 40, 42, 43, 47).

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 1 week after surgery, with serum osteocalcin levels normalising only 6 months after successful parathyroidectomy (31). In three of 51 patients with extreme osteopenia, bone turnover markers remained elevated for 1 year after successful parathyroidectomy (31).

Radiological changes associated with HBS

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, 43, 45, 47) 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, 47).

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 mineralisation 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 normalisation of uptake in the remaining lesions 1 year after parathyroidectomy (16).

Management of HBS

The treatment of HBS is aimed, in the short term, primarily at replenishing the depleted skeletal calcium stores. The first case reports of a HBS, which appeared in the late 1970s, 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 ≤ 1.3 mmol/l was 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 g/day (17, 21, 23, 29, 40, 43, 44). 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 alfacalcidol (2–4 μg/day) (17, 21, 22, 23, 38, 42, 43, 44), 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, 43). In 11 of 18 cases, serum magnesium level was not mentioned, and in one of 18 cases serum magnesium level was within the normal range (16, 18, 21, 23, 24, 25, 27, 29, 40, 41, 42, 44).

Treatment options to prevent HBS

Preoperative treatment with vitamin D Depleted vitamin D status has been postulated to be a risk factor for the development of HBS and it has generally been recommended to supplement vitamin D to normalise 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 HBS (1, 38).

Preoperative treatment with bisphosphonates Two case reports of patients with extensive hyperparathyroid bone disease demonstrated that preoperative treatment with i.v. pamidronate given at a dose of 30 mg for 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, 48). 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 HBS post-operatively (49).

In a retrospective study, Lee *et al.* (37) also demonstrated that none of six patients who had received bisphosphonates preoperatively (either oral clodronate 400–1600 mg/day or i.v. pamidronate 60 mg/day) developed HBS post-operatively, compared with nine of 17 patients who had not been preoperatively treated with bisphosphonates. There was no significant difference in preoperative 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 i.v. zoledronate preoperatively, also reported a low frequency of post-operative HBS of only 4% (35). Another retrospective case series of six patients with radiological features of osteitis fibrosa cystica, who were preoperatively treated with bisphosphonates (oral alendronate 20–30 mg/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 i.v. calcium supplementation (47).

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 i.v. pamidronate combined with calcitriol 1–2 µg/day was able to significantly decrease (but not normalise) serum alkaline phosphatase levels (1600 to 420 U/l) but was not able to completely prevent HBS (42). Four other case reports also show that treatment of severe hyperparathyroidism with alendronate (70 mg/week), pamidronate (twice 90 mg or 5×15 mg i.v.) or zoledronate (twice 4 mg i.v.) was unable to completely prevent HBS (23, 38, 43, 44).

Preoperative treatment with active metabolites of vitamin D Boyle *et al.* (50) showed that preoperative treatment of severe hyperparathyroidism with $1,25(OH)_2D$ (calcitriol) at a dose of 2 µg/day for 1–10 weeks significantly decreased preoperative alkaline phosphatase levels in three of seven patients with radiological bone cysts, and three other patients required little i.v. calcium supplementation to a total of <1 g in the first 12 post-operative days. In contrast, Heath *et al.* (4) showed that six patients with PHPT and radiological evidence of bone involvement, who were treated preoperatively with 2 µg/day of $1,25(OH)_2D$ 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 preoperatively (two of six vs one of six respectively).

Discussion

HBS is a relatively uncommon complication of parathyroidectomy for severe PHPT associated with preoperative high bone turnover. It is characterised by a rapid, profound and persistent hypocalcaemia associated with hypophosphataemia, hypomagnesaemia and is exacerbated by suppressed PTH levels. The duration of the HBS is the time taken to remineralise the skeleton, which is also mirrored by normalisation 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 (51) and may last for up to 12 weeks after initiation of treatment. In contrast to the case with the HBS of severe PHPT, in treated hyperthyroidism, hypocalcaemia is associated with appropriate significant increases in PTH levels (52, 53).

Our literature search suggests that the prevalence of HBS has decreased in the Western World over the last two decades, most likely due to the early detection of still asymptomatic PHPT 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, 45), although exact numbers are missing.

One of the identified risk factors for a post-operative HBS is older age at the time of surgery. With older age being more often associated with vitamin D deficiency, a decrease in renal 1α-hydroxylase activity and lower dietary calcium intakes (1), all three factors potentially contribute 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 (7). A testable hypothesis for the development of bone disease, and for the development of HBS, relates to the possibility that low circulating levels of $1,25(OH)_2D$ with resultant decreased fractional absorption of calcium, leads to undermineralisation of the skeleton (1, 4). Low levels of $1,25(OH)_2D$ may thus represent a measurable risk factor for the development of HBS, independently of age, although 25(OH)D deficiency has been proposed to be the more significant risk factor (38).

Preoperative serum alkaline phosphatase levels reflect the state of bone turnover and, therefore, the degree of osteoclast activity and bone resorption. It has been suggested that preoperative serum alkaline phosphatase concentrations may predict the degree and duration of hypocalcaemia after successful parathyroidectomy (46). Other risk factors for the development of HBS include evidence of bone disease, such as osteitis fibrosa cystica, subperiostal bone erosions or bone cysts (4, 15, 16, 17, 26, 27, 31, 39) and the volume and weight of the removed hyperactive parathyroid gland(s) (1, 3).

Treatment of the HBS is aimed in the short term primarily at replenishing the circulating calcium deficit, and in the longer term, at normalising bone turnover and remineralising the skeleton. Doses of calcium and active vitamin D preparations required and duration of treatment is guided by serum calcium and bone turnover marker levels, aiming at normalisation of bone turnover (3, 15, 20, 26, 27, 28, 45), 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 i.v. administration is often required (15, 17, 21, 22, 23, 29, 40). When calcium-containing solutions are given intravenously, administration into large veins or via a central venous catheter is recommended to minimise 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 (54). In prescribing oral calcium preparations, it is important to realise that different calcium preparations contain different amounts of elemental calcium. Of the available oral preparations, calcium carbonate has the highest percentage of elemental calcium (40%), followed by citrate salts (20%). Other calcium preparations are also available (calcium lactate (13%), calcium gluconate (9%) and calcium glubionate (6.6%)), 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 (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, 27, 28, 45).

Depleted vitamin D status has been postulated to be associated with an increased risk of developing postoperative hypocalcaemia and HBS (55, 56, 57, 58). Preliminary data suggest that preoperative correction of vitamin D deficiency may decrease levels of PTH and bone turnover, without exacerbating hypercalcaemia (55, 58, 59). Although the effect of preoperative vitamin D treatment on post-operative hypocalcaemia has not been evaluated by randomised controlled intervention studies in PHPT, it is our experience that a preoperative replete vitamin D status is associated with a decreased likelihood of a severe or prolonged HBS (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 remodelling sites, thus resulting in refilling of remodelling space and increasing mineralisation of bone (38, 60, 61), In this context, preoperative bisphosphonate treatment would have a potential beneficial effect on the severity and duration of HBS by significantly decreasing or normalising bone turnover before surgery is attempted (38, 48). In contrast, short term preoperative treatment may exacerbate post-operative hypocalcaemia by just reducing bone resorption, without allowing time for a coupled decrease in bone formation. There are as yet no prospective studies or randomised control trials addressing the use of bisphosphonates in the prevention or limitation of duration of HBS. Data from case reports and small case series on the beneficial effect of preoperative treatment with bisphosphonates on the HBS in patients with hyperparathyroid bone disease (7, 35, 37, 51) or with longstanding severe PHPT (49) are conflicting (23, 27, 35, 36, 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, as serum alkaline phosphatase levels had not normalised before surgery (23, 38, 42, 43, 44).

Because low levels of $1,25(OH)_2D$ are a risk factor for the development of post-operative HBS (1, 4), it has also been hypothesised that preoperative

supplementation of $1,25(OH)_2D$ could shorten symptomatic hypocalcaemia and hospital course (1, 7, 50). Data on preoperative $1,25(OH)_2D$ supplementation in patients undergoing parathyroidectomy for severe PHPT are also conflicting (4, 50). A major limitation of studies, addressing the effect of bisphosphonates and/or active vitamin D preparations on the prevention of HBS, is the lack of patient randomisation.

Conclusion

HBS is a relatively uncommon but serious complication of parathyroidectomy for PHPT associated with high bone turnover. There are no clear guidelines for the management of the HBS, 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 normalisation of bone turnover are required for resolution of the hypocalcaemia which may last for a number of months after successful surgery. Adequate preoperative treatment with bisphosphonates may reduce the severity and duration of post-operative hypocalcaemia. Further prospective studies are needed to optimise pre- and post-operative treatment strategies in patients with PHPT and skeletal manifestations at high risk for HBS.

Declaration of interest

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