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

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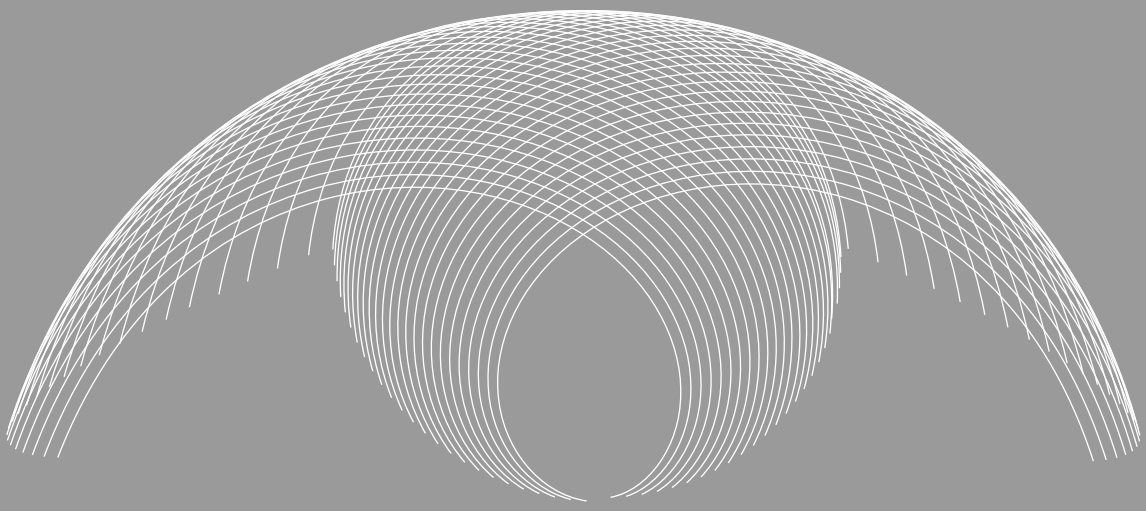

ABSTRACT

The term hungry bone syndrome refers to the rapid, profound and prolonged hypocalcaemia associated with hypophosphataemia, hypomagnesaemia and functional hypoparathyroidism, which follows parathyroidectomy in patients with severe hyperparathyroidism and preoperative high bone turnover. It is a relatively uncommon, but serious adverse effect of parathyroidectomy in patients with severe primary hyperparathyroidism and skeletal manifestations. 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 bone resorption and activation frequency, in the face of continuing bone formation, 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 fibrosia 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.

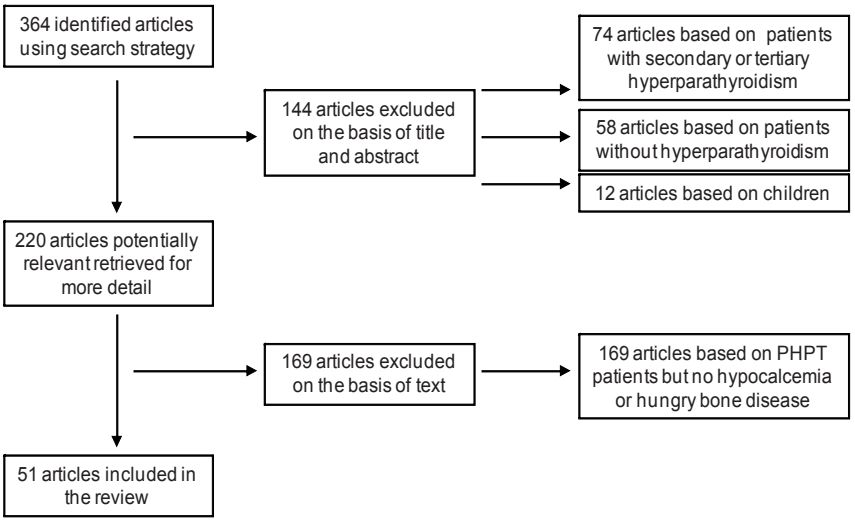

Figure 1. Flowchart of articles included in the systematic review

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, before new bone is formed, which lasts about 3 months. The remodeling 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 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, and on the average difference between the amount of bone resorbed and not yet reformed at each remodeling site, which is largely unchanged in hyperparathyroidism. In severe hyperparathyroidism. The increase in bone resorption leads to mineral depletion of bone and significantly contributes to the hypercalcaemia characteristically observed in patients with hyperparathyroidism (10-14). In patients with hyperparathyroidism and pre-operative high rates of bone turnover, successful parathyroidectomy curbs

osteoclastic resorption, leading to a decrease in the activation frequency of new remodeling sites and to a decrease in remodeling space, leading to a consequent gain in bone mass.

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 $\leq$ 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 from a 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 serie 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 the time of surgery is a risk factor for hungry bone syndrome (1). Brasier *et al.* (1), showed in a group of 198 PHPT patients, that patients who developed hungry bone syndrome were 10 years older than patients with an uncomplicated post-operative course (61 ± 3 vs. 51 ± 1, $P<0.05$).

Table 1. Pre-operative laboratory data

Laboratory investigation	Author	Patients who developed HBS	Patients who did not develop HBS	*P*-value
s-Calcium (mmol/l)	Brasier[1]	3.00 ± 0.05	2.88 ± 0.03	*<0.05*
	Spiegel[36]	3.25 ± 0.05	3.00 ± 0.03	*<0.001*
	Heath[39]	3.94 ± 0.38	2.95 ± 0.15	*<0.01*
	Lee[37]	3.00 ± 0.1	3.00 ± 0.08	*0.7*
s-PTH (pmol/l)	Brasier[1]	10.2 ± 2.00	5.7 ± 0.3	*<0.05*
	Lee[37]	30.7 ± 10	32.9 ± 6	*0.2*
s-alkaline phosphatase (U/l)	Brasier[1]	68 ± 15	38 ± 2	*<0.05*
	Heath[39]	51 ± 37	12 ± 6	*<0.01*
	Lee[37]	248 ± 48	169 ± 31	*0.1*

HBS: hungry bone syndrome, s: serum

Laboratory investigations prior to surgery

Patients who developed hungry bone syndrome had higher pre-operative levels of serum calcium (3.00 ± 0.05 vs. 2.88 ± 0.03 mmol/l, $P<0.05$ and 3.25 ± 0.05 vs. 3.00 ± 0.03 mg/dl, $P<0.001$ and 3.94 ± 0.38 vs. 2.95 ± 0.15 mmol/l, $P<0.01$) and almost 2-fold increased levels of PTH (10.2 ± 2 vs. 5.7 ± 0.3 pmol/l, $P<0.05$) and of alkaline phosphatase (68 ± 15 vs. 38 ± 2 IU/l, $P<0.05$ and 12 ± 6 vs. 51 ± 37 U/dl, $P<0.01$) 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 calcium levels (3.00 ± 0.1 vs. 3.00 ± 0.08 mg/dl, $P=0.7$), PTH (30.7 ± 10 vs. 32.9 ± 6 pmol/l, $P=0.2$) or of alkaline phosphatase (248 ± 48 vs. 169 ± 31 IU/l, $P=0.1$) levels 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 (1.5 ± 0.1 vs. 1.7 ± 0.04 mEq/l, $P<0.001$ and 3.9 ± 0.1 vs. 4.3 ± 0.04 g/dl, $P<0.001$, respectively) (1).

There were no data available 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 (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 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 a hungry bone disease (4,16,17,26,27,31,40), which also reflects prolonged exposure of the skeleton to high circulating PTH levels. Fourteen of 18 available 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). Hungry bone syndrome was reported in 25-90% of patients with radiological evidence of PHPT-related bone disease versus in 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.* (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 relation between histological characterizations 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 for sometimes 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).

Table 2. Details of pre-operative treatment with bisphosphonates to prevent post-parathyroidectomy hungry bone syndrome

Author	No. of patients	Radiological evidence of bone involvement	Pre-operative treatment	%HBS
Franca, 2011[50]	6	Osteitis fibrosa cystica	Alendronate 20-30mg/day for 4-6 weeks or pamidronate once once 90 mg iv or ibandronate 150 mg iv	0
Yong, 2010[44]	1	Fracture, extensive osteitis fibrosa cystica, lytic lesions, osteoporosis	Pamidronate twice 90 mg iv	100
Corsello, 2010[45]	1		Zoledronate twice 4 mg	
Gurevich, 2008[52]	1	Not mentioned	Pamidronate 3 times 30 mg and once 90 mg iv	0
Malabu, 2007[35]	46	46% had bone aches	Zoledronate	4
Demirci, 2007[23]	1	Osteoporosis, loss of subperiosteal cortex	Alendronate 70 mg for 2 weeks	100
Lee, 2006[37]	23	Not specified	Pamidronate 60-1600 mg/day for 1-17 days or clodronate 300 iv for 1-15 days with or without 1600 mg/day p.o. for 3-7 days vs. no bisphosphonate	0 vs. 53
Hisham, 2000[43]	1	Extensive metabolic bone changes	Pamidronate once 60 mg iv	100
Graal, 1998[38]	1	Low BMD, vertebral fractures	Pamidronate 15 mg/day iv for 5 days, followed by twice daily 150 mg orally	100
Kumar, 1996[51]	1	Extensive metabolic bone changes	Pamidronate twice 30 mg iv	0
Brossard, 1993[7]	1	Osteopenia, subperiosteal bone resorption, multiple osteolytic lesions	Pamidronate once 60 mg iv	0

HBS: hungry bone syndrome, BMD: bone mineral density

Table 3. Details of post-operative treatment of patients who developed hungry bone syndrome after parathyroidectomy

Author	Age/ Sex	Radiological signs of PTH-induced bone disease	Pre-operative treatment	Post-PTx calcium (min)	Post-operative treatment (maximum dose per day)
Silaghi, 2011[25]	48/F	Osteolytic lesions, resorption of distal phalanx of fingers			Calcium, vitamin D and bisphosphonates
Kim, 2011[24]	29/F			1.78 mmol/l	Calcium iv and orally
Corsello, 2010[45]	64/F		Zoledronate twice 4mg/day, calcitonin 400 IU/day	1.0 mmol/l	Calcium gluconate 6-8 g/day iv, calcitriol 3 ug/day (transient 1.5 ug/day iv)
Yong, 2010[44]	23/M	Fracture, extensive osteitis fibrosa cystica, lytic lesions, osteoporosis	Pamidronate twice 90 mg iv	2.0 mmol/l	Calcium iv and orally total 11.4 g/day, calcitriol 2 ug/day, magnesium iv and orally
Ajmi, 2010[16]	48/F	Diffusely increased scintigraphic uptake, radiolucent lesions		1.5 mmol/l	Calcium iv, vitamin D orally
Hussain, 2008[21]	25/F	General loss of bone density, old fractures, healed with malunion		1.9 mmol/l	10% Calcium gluconate 10 ml iv, calcitriol 3 ug orally
Rathi, 2008[17]	45/F	Subperiostal erosions, brown tumors, chondrocalcinosis		1.83 mmol/l	Elemental calcium 2.5 g iv and 8 g orally, calcitriol 4 ug orally, magnesium orally
Demirci, 2007[23]	53/F	Subperiostal erosions, salt and peper skull, lytic lesions	Alendronate 70mg/week, calcitriol 0.5 ug/day	1.4 mmol/l	Elemental calcium 720 mg iv and 14 g orally, and calcitriol 2 ug orally
Meydan, 2006[42]	52/F	Multiple lytic lesions, foci of increased scintigraphic uptake			Calcium and vitamin D
Kuzucu, 2002[18]	50/F	Multiple foci of intense scintigraphic uptake	Bisphosphonates	1.6 mmol/l	Calcium iv and orally, calcitriol
Hisham, 2000[43]	36/M	Florid skeletal changes	Calcitonin 600 mg for 2	1.8 mmol/l	Calcium iv and 4 g orally, calcitriol 2 ug

			weeks, calcitriol 1 ug pamidronate 60 mg iv		
Graal, 1998[38]	34/F	Osteoporosis, vertebral fractures	Pamidronate 75 mg iv twice daily 150 mg orally	1.79 mmol/l	Calcium iv 1.6 g/day, calcitriol 2 ug/day, magnesium iv and orally
Chen, 1996[19]	20/F	Generalized osteoporotic changes, subperiosteal erosions, multiple brown tumors		1.17 mmol/l	Calcium, phosphorus and magnesium supplementation
Varthakavi, 1985[29]	44/F	Focal osteolytic lesions, periosteal erosions, osteosclerosis, fracture		1.17 mmol/l	Calcium gluconate 144 ml iv
Laitinen, 1977[41]	69/F			1.6 mmol/l	Calcium 10 g iv
Scott, 1976[22]	35/M	Widespread demineralization		1.3 mmol/l	10% Calcium gluconate 20 ml iv, calcium 12 g, orally magnesium chloride iv, calciferol 2.5 ug orally
Falko, 1976[15]	19/M	Deossification of skull, Subperiosteal erosions, and demineralization		1.3 mmol/l	Calcium gluseptate 30 g iv, 50% magnesium sulfate 5 ml im, vitamin D 150.000 Units/day
Jones, 1973[26]	67/F			1.2 mmol/l	Calcium iv and orally, 200 mg magnesium sulphate iv
Ahuja, 1968[27]	38/F	Multiple fractures, cystic changes and mottling, subperiostal erosions			Calcium 4 Gm/day iv and 12 Gm/day orally vitamin D 1.200.000 Units/day

PTH: parathyroid, PTx: parathyroidectomy, iv: intravenous

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). Scintigraphy shows an increased uptake 1 month after parathyroidectomy, known as "flare phenomenon", which reflects a healing response due to a significant increase in bone formation with a 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 following withdrawal of the effect of high circulating levels of PTH on the skeleton. 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). Severely decreased serum calcium levels of $\leq$1.3 mmol/l were reported despite treatment with very high doses of calcium, magnesium and cholecalciferol (15,26,27). However, difficulties in the management of hungry bone syndrome are still being reported, also after active metabolites of vitamin D and their synthetic analogues became available for use in the clinic (23).

The amount of elemental calcium supplementation required to treat the severe hypocalcaemia varies between 8 and 12 grams per day (17,21,23,29,41,44,45). Initially calcium is supplemented intravenously, followed by oral preparations, with lower doses of calcium being possible because of concomitant use of active metabolites of vitamin D, in the form of calcitriol or alfacalcidol (2 to 4 ug per day) (17,21-23,38,43-45), and after replenishing magnesium stores as required. The

amount of magnesium required to correct hypomagnesaemia is not always reported and supplementations has been variably given in the form of intravenous magnesium chloride or sulphate or oral 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 levels were 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 of hungry bone syndrome (1,38).

Pre-operative treatment with bisphosphonates

Two case reports of patients with a short history of PHPT, but with extensive hyperparathyroid-related bone disease, who were treated with either pamidronate i.v. 30 mg on 2 consecutive days or with a single infusion of 60 mg once, demonstrated that serum calcium decreased pre-operatively and that patients needed much less (1500 mg of elemental calcium orally per day) or no calcium supplementation post-operatively (7,51). One case report showed that a patient with a history of severe PHPT for > 8 years who received alendronate for 6 years, in addition to a total of 180 mg pamidronate i.v. pre-operatively, 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 clodronate 300-1600mg/day or pamidronate 60mg/day) developed hungry bone syndrome post-operatively, compared to 9 of 17 patients who had not received bisphosphonates pre-operatively (Table 2). There were no significant differences 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 serie of 46 patients with severe bone disease, who were treated with intravenous zolidronate pre-operatively also reported a low frequency of hungry bone syndrome of only 4% (35). Another retrospective case serie of 6 patients with radiological characteristics of osteitis fibrosa cystica, who were pre-operatively treated with bisphosphonates (alendronate 20-30mg/day for 4-6 weeks or a single dose of pamidronate 90 mg i.v. or ibandronate 150 mg i.v.) reported that none of the patients needed intravenous supplementation of calcium post-operatively (50).

In contrast, a case report of a patient with severe, prolonged and extensive bone involvement (florid metabolic bone changes on X-ray), has shown that a single dose of 60 mg pamidronate i.v. 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 not able to completely prevent a hungry bone syndrome (43). Four others cases have also shown that treatment of severe hyperparathyroidism with alendronate (70 mg/week), pamidronate (twice 90 mg i.v. or 5 times 15 mg i.v.) or zolendronate (twice 4 mg i.v.) was unable to completely prevent a hungry bone syndrome (23,38,44,45).

Pre-operative treatment with active metabolites of vitamin D

Boyle *et al.* (53) showed that pre-operative treatment of severe hyperparathyroidism with 2 µg/day of $1,25(OH)_2D$ for 1-10 weeks significantly decreased pre-operative alkaline phosphatase levels in 3 of 7 patients with prominent radiologically apparent bone cysts, and 3 other patients required intravenous calcium 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 $1,25(OH)_2D$ 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 pre-operative (2 of 6 vs. 1 of 6, respectively).

DISCUSSION

Hungry bone syndrome is characterized by a rapid, profound and persistent hypocalcaemia associated with functional hypoparathyroidism, which follows parathyroidectomy in patients with severe primary hyperparathyroidism and preoperative high bone turnover. 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, healing of radiological features of osteitis fibrosa cystica and brown tumours and by significant gains in bone mass.

Hungry bone syndrome should be distinguished from the relatively common short- or longer-term hypocalcaemia encountered after thyroid surgery due to temporary or permanent hypoparathyroidism and from the temporary hypocalcaemia often observed after parathyroidectomy for primary hyperparathyroidism with no or marginally increased bone turnover pre-operatively, which resolves spontaneously or readily after supplementation of active vitamin D until recovery of parathyroid function. In the context of primary hyperparathyroidism, a prerequisite for developing a hungry bone syndrome is a severely increased bone turnover state prior to surgery. A period of functional hypoparathyroidism may be followed by a period of increased PTH levels, more often encountered and exacerbated by associated vitamin D deficiency. These increased PTH levels are however unable to correct the hypocalcaemia, which will only resolve after adequate mineralization of the skeleton and normalization of bone turnover, often requiring huge doses of active metabolites or analogues of vitamin D and of calcium supplements, for periods sometimes exceeding 12 months after successful surgery.

Our literature search suggests that over the last 2 decades the prevalence of hungry bone syndrome has decreased in the Western World, most likely due to the early detection of still asymptomatic primary hyperparathyroidism by routine calcium screening before the advent of clinically evident bone disease, such as osteitis fibrosa cystica (38,49), although exact numbers are missing.

One of the identified risk factors for a post-operative hungry bone syndrome is the older age at the time of surgery, with age being associated with vitamin D deficiency, a decrease in 1α-hydroxylase activity, and lower dietary calcium intakes (1), all 3 factors 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, due to high levels of serum calcium which directly inhibit renal 1α-hydroxylase production, but may also result in renal impairment and further decrease in 1α-hydroxylase activity (54). 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 (55). Radiological evidence of bone disease, in the form of osteitis fibrosa cystica, subperiostal bone erosions or resorption or bone cysts, has also been stated to be a risk factor for the development of hungry bone disease (4,15-17,26,27,31,40). Pathological risk factors include the volume and weight of the removed adenoma(s), which have been found to be significantly greater in patients who developed a hungry bone syndrome compared to patients who had an uncomplicated post-operative course (1,3).

Treatment of the hungry bone syndrome is aimed in the short term primarily at replenishing the circulating calcium deficit, resulting from the increased utilisation of calcium arising from the abrupt cessation of bone resorption by the removal of the stimulatory effect of PTH in the face of continuing bone formation to refill the multiple resorption cavities. In the longer term, treatment is aimed at restoring

calcium homeostasis by substituting the temporarily missing stimulatory effect of PTH on the 1α-hydroxylase enzyme by providing the active form of vitamin D to ensure adequate intestinal absorption of calcium. Doses and duration of treatment are guided by serum calcium levels and achievement of normalisation of bone turnover (3,15,20,26-28,49), which can sometimes exceed 12 months after successful surgery.

It is estimated that 10 grams of calcium daily is on average necessary to restore and maintain serum calcium within the normal range (15,17,21-23,29,41). Lower doses of calcium are possible because of concomitant use of active metabolites of vitamin D, in the form of calcitriol or alfacalcidol (2 to 4 ug per day) (17,21-23,38,43-45), or very occasionally higher doses (unpublished personal observations). The reason for this is post-operative low PTH levels which can last for up to 6 months after parathyroidectomy, resulting in lack of stimulation of the 1α-hydroxylase enzyme.

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. Parenteral calcium could be initially administered intermittently, for example in the form of one or two 10 ml ampoules of 10% calcium gluconate diluted in 50-100 ml of 5% dextrose infused slowly over 10 minutes. Continuous administration of a diluted solution of ten 10 ml ampoules of 10% calcium gluconate in 1 litre of 5% dextrose or 0.9% saline is often subsequently required to prevent recurrence of hypocalcaemia. This is given at an initial infusion rate of 50 ml/hour, slowing down as required, aiming at maintaining serum calcium at least at the lower end of the reference range. Electrocardiographic monitoring is recommended as dysrhythmias may occur in case of too rapid correction of the hypocalcaemia (56)

Of the available oral calcium preparations calcium carbonate has the highest % of elemental calcium (40%), followed by citrate salts (20%). If a patient cannot tolerate these calcium supplements, other calcium preparations are 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 glubionate (6.6%) (20). Oral calcium therapy should be initiated as soon as practical, but should always be combined with active vitamin D metabolites or analogues such as calcitriol or alfacalcidol to ensure adequate intestinal absorption of the administered oral preparation.

Treatment of hypomagnesaemia depends on the degree of magnesium deficiency. When high doses of magnesium are required, this should only be given intravenously in adequate dilutions of magnesium sulphate, and not orally or intramuscularly. 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).

The severity of a hungry bone syndrome is dictated by the degree of bone resorption pre-operatively, the highest pre-operative bone turnover being associated with the most severe and prolonged hungry bone syndrome. Preventive measures for a hungry bone syndrome should thus aim at reducing bone turnover pre-operatively. This should be first achieved by correcting any prevailing vitamin D deficiency. Depleted vitamin D status has been postulated to be associated with an increased risk of developing postoperative hypocalcaemia and hungry bone syndrome (57-60). Preliminary data suggest that pre-operative correction of vitamin D deficiency may decrease levels of PTH and bone turnover, without exacerbating hypercalcaemia (57,60,61). 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.

Bisphosphonates are potent antiresorptive agents widely used in the management of bone disorders associated with increased bone turnover, such as Paget's disease of bone or metastatic bone disease. These agents inhibit osteoclastic bone resorption, decrease activation frequency of remodeling sites, resulting in refilling of remodeling space and increased mineralization of bone. Bisphosphonates have been shown to reduce bone turnover in severe

hyperparathyroid bone disease (38,62,63). 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 (38,64). 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. There are, however, case reports and small case series of patients with extensive hyperparathyroid-related bone disease (35,37,54,64) or with longstanding severe PHPT (52) who received pamidronate pre-operatively and did not develop a hungry bone syndrome post-operatively (23,27,35-37). Other case reports have shown that pamidronate combined with calcitriol decreased serum alkaline phosphatase levels, but was unable to completely prevent a hungry bone syndrome in patients with severe, prolonged and extensive bone involvement (23,38,43-45). However, in these case reports, the duration of pre-operative treatment with bisphosphonates and of active vitamin D was deemed to be too short and the dosage to low, since serum alkaline phosphatase levels had not normalized before surgery (23,38,43-45).

Because low levels of $1,25(OH)_2D$ 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 $1,25(OH)_2D$ could shorten symptomatic hypocalcaemia and hospital course (1,53,54). Data on the results of $1,25(OH)_2D$ supplementation are, however, conflicting (4,53). A major limitation of the studies looking at prevention of hungry bone syndrome, using either bisphosphonates or $1,25(OH)_2D$ supplementation or both, is the lack of patient randomization.

CONCLUSION

Hungry bone syndrome is a relatively uncommon, but serious complication of parathyroidectomy for severe 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 correcting the effects of the functional hypoparathyroidism by using high doses of calcium and 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. 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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