Changes in bone turnover markers in primary hyperparathyroidism and response to surgery

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ABSTRACT

INTRODUCTION Involvement of the bone is common in primary hyperparathyroidism. The aim of the study was to assess bone turnover markers in response to surgery for primary hyperparathyroidism.

METHODS This was a retrospective study of patients diagnosed and treated for parathyroid disease between 2005 and 2012. Interventions studied were surgery and medical treatment. The main outcome measures studied were serum levels of calcium, intact parathyroid hormone (iPTH), bone-specific alkaline phosphatase, N-terminal cross-linking propeptide of type 1 procollagen (P1NP) and C-terminal cross-linking telopeptides of type I collagen (CTX), both pre- and postoperatively at 6 months and 1 year; bone mineral density (at the spine and hip assessed by dual-energy x-ray absorptiometry after 1 year of treatment).

RESULTS A total of 122 (110 female, 12 male) patients (age range 25–91 years) underwent treatment for parathyroid disease during the study period; 30 patients were treated conservatively and 92 proceeded to surgery following localisation studies. Following surgical intervention, P1NP dropped significantly from a mean of 64.68 ng/ml (standard deviation, SD $\pm$ 68.07 ng/ml) preoperatively to 26.37 ng/ml (SD $\pm$ 20.94 ng/ml) and CTX from 0.69 pg/ml (SD $\pm$ 0.44 pg/ml) to 0.15 pg/ml (SD $\pm$ 0.16 pg/ml) at 6–12 months ($P < 0.0001$). This change was reflected in improvement in bone mineral density (T scores) of the hip and spine by 43% ($P < 0.03$) and 38% ($P < 0.01$), respectively, following surgery. In patients treated conservatively ($n = 30$), there was no improvement either in the bone turnover markers or bone densitometry scans.

CONCLUSIONS Surgery improves bone density in patients with parathyroid disease. Improvement in serum bone turnover markers is seen following parathyroidectomy. The association with bone density needs further evaluation in larger studies.

KEYWORDS

Primary hyperparathyroidism – Surgery – Parathyroidectomy

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Introduction

Primary hyperparathyroidism is a disorder of one or more of the parathyroid glands leading to a state of increased bone turnover because of inappropriate parathyroid hormone secretion. The spectrum of the disease has changed in the 21st century and more patients are being diagnosed with asymptomatic parathyroid disease;¹ previously, patients frequently presented with symptoms of bone problems. However, the choice of treatment (surgery or a conservative approach) is dictated by the presence or absence of symptoms and complications associated with the disease.

Patients with primary parathyroid disease have reduced bone mineral density in the cortical bones demonstrable by densitometry studies and markers of bone turnover.^{2,3} Markers of bone formation, usually the products of osteoblast activity, can be assessed by measuring alkaline phosphatase (ALP) and bone-specific alkaline phosphatase and N-terminal propeptides of type 1 procollagen (P1NP). In the case of bone resorption markers, collagen breakdown

products are usually measured in the circulation or urine. Some examples include deoxypyridinoline (DPD), C-terminal cross-linking telopeptides of type I collagen (CTX) and hydroxylysine glycosides. The more commonly measured bone formation marker is P1NP and bone resorption marker is CTX.

Bone turnover markers have been shown to be elevated in parathyroid disease, especially in patients who are symptomatic.^{4,5} Activity has also been shown to be at the upper limits of normal or elevated in asymptomatic disease.⁶ The aim of this study was to study the effects of surgery on bone turnover markers in patients with primary hyperparathyroidism.

Methods

This was a retrospective study of 122 consecutive patients treated for parathyroid disease between 2005 and 2013. Patient demographic data were collected together with biochemical markers of assessment and include serum

calcium, intact parathyroid hormone, bone-specific alkaline phosphatase, P1NP and CTX were measured serially. Patients with bone disease underwent bone densitometry preoperatively and at 1–2 years following intervention.

Outcomes measured were cure, improvement in bone turnover markers and improvement in bone density on dual-energy x-ray absorptiometry (DEXA) at 1–2 years post-intervention. Patients with vitamin D deficiency were treated before intervention. In this cohort, 30 patients were treated conservatively with bisphosphonates because of poor fitness for surgery; these patients were included in the analysis. Patients with renal hyperparathyroidism and children were excluded from the study.

Patients underwent surgery in the form of open-neck exploration, minimally invasive parathyroidectomy (where disease was localised) and video-assisted thoracoscopic surgery where disease was localised to the mediastinum. The procedures were performed under general anaesthesia. Pathological data of the excised glands and postoperative complications were collected.

Descriptive statistics are presented as means and standard deviation (SD) for continuous variables. The data collected were analysed using Windows SPSS, version 17. Associations between various parameters assessed were with linear regressions and presented with correlation coefficients and *P*-values. The level of significance was *P* < 0.05.

Results

A total of 122 patients (110 female, 90%; 12 male, 10%; age range 25–91 years) were diagnosed with parathyroid disease, of whom 92 underwent surgery. The mean age of the cohort was 66.7 years (SD ± 11.8 years); 82 patients (67%) were symptomatic (11 with mild and 71 with moderate or severe symptoms) and 40 (33%) were asymptomatic. Medical treatment was considered in 30 patients (25%) who were deemed not fit for surgery even under local

anaesthesia and sedation or patient preference for medical treatment.

Of the 92 patients who underwent surgery, 56 (61%) had open parathyroidectomy, 34 (37%) focused exploration and 2 (2%) underwent video-assisted thoracoscopic surgery. In 90 patients (98%), surgical parathyroidectomy achieved a cure and 2 patients had persistent disease. In terms of complications from surgery, one (1%) patient had permanent recurrent laryngeal nerve palsy, seven (8%) patients had temporary hypocalcaemia, with no patient having permanent hypoparathyroidism. The temporary hypocalcaemia was treated with oral calcium supplementation. Pathology of the excised gland showed an adenoma in 91 patients (99%) and hyperplastic disease in 1 patient (1%).

The change in bone turnover markers in patients treated with surgery is shown in Table 1. There was a significant drop in CTX and P1NP post-parathyroidectomy at 6–12 months post-surgery. P1NP dropped from a mean of 64.68 ng/ml (SD ± 68.07 ng/ml) preoperatively to 26.37 ng/ml (SD ± 20.94 ng/ml) following surgery, which corresponds to a 61% drop (*P* < 0.0001). CTX dropped from a mean of 0.69 pg/ml (SD ± 0.44 pg/ml) to 0.15 pg/ml (SD ± 0.16 pg/ml), corresponding to a 78% drop in preoperative values (*P* < 0.0001). Serum bone alkaline phosphatase dropped by a value of 14% from a mean preoperative level of 76.5 ng/ml (SD ± 26.5 ng/ml) to a postoperative level of 65.55 ng/ml (SD ± 20.89 ng/ml; *P* < 0.0027). The drop in P1NP is seen maximally at 6 months and the corresponding drop in CTX at 12 months.

The effect of surgery whereby the catabolic effect of excess parathyroid hormone on the bone is negated is shown by the improvement in DEXA scan after 12 months. The results are summarised in Table 2. The mean T-score of spine and hip improved by 43% (*P* < 0.03) and 38%, (*P* < 0.01), respectively, following surgery. The short-term changes in bone turnover appeared to correlate with improvements in P1NP and CTX levels (*P* < 0.001) in

Table 1 Pre- and postoperative bone turnover levels in the study cohort (N = 122)					
Parameter	Bone turnover				P-value
	Preoperative		Postoperative		
	Value	SD	Value	SD	
Treated surgically (n = 92)					
P1NP (ng/ml)	63.36	± 67.66	26	± 21.97	< 0.0001
CTX (pg/ml)	1.9	± 0.44	0.14	± 0.16	< 0.0001
Bone ALP (ng/ml)	76.5	± 26.5	65.55	± 20.89	< 0.027
Treated medically (n = 30)					
P1NP (ng/ml)	56.34	± 31.46	31.11	± 16.35	< 0.003
CTX (pg/ml)	0.61	± 0.36	0.34	± 0.18	< 0.001
Bone ALP (ng/ml)	73.66	± 22.8	78.88	± 29.39	< 0.485
ALP, alkaline phosphatase; CTX, C-terminal cross-linking telopeptides of type I collagen; P1NP, N-terminal cross-linking propeptide of type I procollagen; SD, standard deviation.					

Table 2 Baseline and 1-year dual-energy x-ray absorptiometry ($N = 122$)

Table 2. Baseline and 1-year follow-up data for energy intake, body composition, and bone mineral density (BMD)					
Bone mineral density	Preoperative		Bone turnover		P-value
	Value	SD	Value	SD	
Treated surgically (n = 92)					
Spine	1.1293	± 1.644	−0.6691	± 1.0842	< 0.03
Hip	1.288	± 1.165	−0.8344	± 0.94	< 0.01
Treated medically (n = 30)					
Spine	1.2523	± 1.114	−1.75	–	< 0.249
Hip	1.6478	± 1.047	−1.5	± 0.7961	< 0.645
SD, standard deviation					

comparison with alkaline phosphatase levels at 1 year. The improvement in bone densitometry scans were seen in patients who had normalised calcium post-surgery.

In 30 patients who did not undergo surgery, treatment was with bisphosphonate therapy in 21 patients; 9 patients completely refused any form of treatment. Calcium levels normalised in six patients with bisphosphonate therapy for a short period of time. In relation to bone turnover markers, P1NP dropped from a mean of 56.34 ng/ml (SD ± 31.46 ng/ml) to 31.11 ng/ml (SD ± 16.35 ng/ml), corresponding to a drop of around 45% ($P < 0.003$) and CTX from a mean of 0.61 pg/ml (SD ± 0.36 pg/ml) to 0.34 pg/ml (SD ± 0.18 pg/ml), corresponding to a drop of 50% ($P < 0.001$; Table 2). There was no improvement in bone mineral density DEXA changes in the spine ($P = 0.2499$) and the hip ($P = 0.645$). Only six patients had their serum calcium normalised with medical treatment with bisphosphonate therapy, a cure rate of 20% in comparison with 98% for surgical treatment. No patient received oral cinacalcet therapy for control of hypercalcaemia.

Discussion

Primary hyperparathyroidism is a disorder of bone metabolism characterised by hypercalcaemia with an inappropriate normal or high levels of parathyroid hormone. In the past, primary hyperparathyroidism was characterised by severe hypercalcaemia, recurrent nephrolithiasis, osteoporosis and osteitis fibrosa cystica (cystic bone destruction).⁷ Over the years, the clinical presentation has changed and more people are diagnosed asymptotically because of better screening tools. However, patients with asymptomatic disease may still be at risk of undiagnosed complications, such as cardiovascular risk, subtle neuropsychological symptoms and osteoporosis. Osteoporotic fractures are a significant cause of morbidity and mortality and bone loss most commonly affects cortical sites.⁷

Markers of bone formation and resorption reflect the skeletal metabolism and are used as indirect tools to assess bone turnover and the extent to which the disease process is active in bone.⁸ Bone formation and resorption markers are

raised, even in asymptomatic patients. Valdemarsson *et al.*, in their series of 30 patients with mild hyperparathyroidism, showed changes in circulating levels of biochemical markers of bone formation and resorption.⁶ Current guidelines advocate surgery as the definitive treatment for patients with symptomatic primary hyperparathyroidism or asymptomatic patients with severe hypercalcaemia, renal failure (estimated glomerular filtration rate less than 60) and those with osteoporosis.⁹

In our cohort, parathyroidectomy effected a cure in 98% of patients. This is in comparison with only 20% of patients treated with medical intervention. Parathyroidectomy is normally associated with an immediate fall in parathyroid hormone levels and normalisation of serum calcium concentration,⁸ which was also observed in this cohort. The benefit of parathyroidectomy on the bones, especially in reduction of fractures, was not studied due to the short period of follow-up. However, Vander Walde *et al.* have shown that parathyroidectomy is associated with decreased fracture risk, irrespective of age and calcium or parathyroid hormone levels.¹⁰ Fifty-eight patients (63%) were found to be vitamin D deficient and required vitamin D replacement, which is similar to rates reported in the literature.^{11,12}

When the bone turnover markers were analysed in our cohort, reductions in both CTX and P1NP markers were seen, with a drop of 61% for P1NP and 78% for CTX post-surgery; however, more a rapid reduction was seen in CTX markers. This is consistent with the hypothesis that the initial anabolic activity of parathyroid hormone affects processes associated with bone formation (P1NP); on the other hand, changes in CTX are delayed for several months, which is the result of bone remodelling by osteoclast activation.⁸

A similar reduction of bone turnover markers was also observed in patients who underwent medical treatment with bisphosphonates and vitamin D replacement. Oral cinacalcet may also cause a reduction of serum calcium and parathyroid hormone over a long period of time¹⁵ but none of our patients received calcimimetic therapy. Bisphosphonates treatment alone can decrease calcium and increase bone mineral density¹⁴ but such an effect was not seen in the small group of patients who were treated conservatively.

The effect of bisphosphonates in the reduction of fracture risk is well documented¹⁵ but their efficacy in comparison with surgery has not been studied.

Parathyroidectomy has been shown to increase bone mineral density in patients with parathyroid disease^{16–18} and this improvement is the result of change from a catabolic state to a state of low bone turnover.^{5,16,19,20} In our cohort, the improvements in bone mineral density of the cortical bone of the spine and hip improved by 38% and 43%, in comparison with patients who were treated medically, where no improvement in bone mineral density was seen, even in patients where calcium and parathyroid hormone levels normalised. The improvement in bone mineral density correlated with the changes in the levels of bone turnover markers, namely P1NP and CTX, and these findings are similar to those reported in the literature.^{6,18,21,22} We followed-up our patients for 3 years but it would be useful to monitor patients for a longer period to see whether the bone turnover markers remain lower and to observe whether the gain in bone mineral density is maintained over the years or the results of surgery are short lived.

The study has some limitations. This is a retrospective cohort study with an inherent selection bias. The study outcomes are short term and did not look at fracture risk and cardiovascular outcomes. Long-term studies would be needed comparing surgery with medical treatment and measurement of bone turnover markers, together with bone densitometry, to assess these risks.

Conclusion

In conclusion, this study shows the short-term beneficial effects of parathyroidectomy on bone turnover markers and changes in bone densitometry. This benefit was seen in both symptomatic and asymptomatic patients. Parathyroidectomy improves bone density and bone turnover markers may predict improvements but the reliability needs to be assessed in larger studies.

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