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Evaluation of changes in biochemical parameters and bone mineral densitometry following parathyroidectomy in patients with primary hyperparathyroidism

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ABSTRACT

Introduction: Parathyroidectomy for primary hyperparathyroidism (PHPT) has been suggested to improve bone mineral density (BMD). To evaluate the changes in BMD and biochemical parameters following parathyroidectomy in patients with PHPT.

Methods: This prospective cohort study included patients with PHPT who were referred to the Endocrine Clinic of a tertiary center between 2017 and 2018. Patients were divided into two groups: surgery (SG) and non-surgery (NSG). BMD and serum levels of calcium, phosphorus, creatinine, 25(OH)D, albumin and parathyroid hormone (PTH) were analyzed at baseline and two years of follow-up.

Results: Thirty patients were included: 20 in the SG and 10 in the NSG. In the SG, significant increases were observed in 25(OH)D and phosphorus levels, while calcium and PTH levels significantly decreased after two years ($p < 0.001$). No significant changes in biochemical parameters were observed in the NSG. In the SG, both T-scores and Z-scores of the lumbar vertebrae significantly increased ($p < 0.01$). In the distal radius, the T-score significantly increased ($p < 0.05$) and the Z-score showed a borderline significant increase ($p = 0.048$). No significant changes in femoral neck BMD were observed in either group. **Conclusion:** Parathyroidectomy in patients with primary hyperparathyroidism improves BMD in the lumbar vertebrae and distal radius and normalizes biochemical parameters.

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Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder that is characterized by elevated or inappropriate serum parathyroid hormone (PTH) levels concluding hypercalcemia and hypophosphatemia[1]. Parathyroid tumors are often solitary adenomas without other endocrinopathies. However, the presentation has changed over time, from a symptomatic disease with bone pain, fractures, nephrolithiasis, and muscle weakness, to a predominantly asymptomatic condition (80-90%); including nonspecific cardiovascular, neuropsychological, cognitive, neuromuscular, rheumatologic, and gastrointestinal symptoms [3, 4].

Parathyroid hormone (PTH) exhibits paradoxical effects on bone including osteoblast differentiation and also increases osteoclastic bone resorption by enhancing osteoclast production [5]. Consequently, PTH increases bone remodelling, exerting a catabolic effect on cortical and, to a lesser extent, trabecular bone and prolonged bone exposure to increased PTH levels results in osteoporosis, fragility fractures, and even skeletal deformities [6]. While osteoporosis is mostly asymptomatic but can be disabling, it is now the major concern related to the PTHP. Although surgical removal of abnormal parathyroid tissue is the definitive treatment of this disease medical care and monitoring without surgery for patients

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with mild and asymptomatic disease, especially in older patients, is still preferred by some physicians and patients [7]. In the present study, we aimed to evaluate the BMD measurement changes in cortical and trabecular bone before and after parathyroidectomy comparing with patients who received only medical managements to evaluate which approach seems to have the greatest benefits while having the least harms.

Materials and methods

Study designation and participation

This is the prospective cohort study included patients referred to our tertiary centre between 2018 and 2019 with primary hyperparathyroidism. The patients were divided to surgery group and non-surgery group according to the surgical criteria of PHPT (with proven histology of parathyroid adenoma postoperatively) [8].

The inclusion criteria defined as: (1) age <50 years, (2) serum calcium levels 1 mg/dl above the upper limit of the normal range (>11.5 mg/dl), (3) glomerular filtration rate (eGFR) < 60 mL/min, (4) history of fragile fracture, and (5)T-score < 2.5 SD. The exclusion criteria were as follows: being unwilling to continue the study, experiencing unsuccessful PTX, using Estrogen and Progestin, and taking bisphosphonates after surgery.

All patients were followed at least two years after the initial visit. The data including demographics information, Serum level of Calcium, Phosphorus, Creatinine, PTH, Albumin, and 25OH vitamin D was measured. The Bone mineral densitometry (by Hologic and Norland DXA machines) of the distal third of the radius, lumbar vertebrae and femoral neck characteristics were noted as t-scores and z-scores. A maximal effort was made to perform the procedure in a single center, preferably with the same operator.

Statistical analysis

The normality of data distribution was evaluated by Kolmogorov-Smirnov test. In the study, non-parametric methods were used for analysis. The changes in bone density before and after surgery were calculated using the *Wilcoxon signed*-rank *test.* Data analysis was performed using SPSS software version 21 and two-sided P- values less than 0.05 were considered statistically significant.

Results

Among our 39 patients with primary hyperthyroidism, 29 patients had history of surgery (surgery group (SG)), 9 patients were excluded from the study; 4 patients had passed away (3 patients due to covid-19 and one patient due to heart attack), 3 patients did not cooperate, and 2 patients were not included in the study according to taking antiosteoporosis medication. There were 10 people in the non-surgery group (NSG), and out of these 10 people, 2 did not have a surgical indication primarily while 8 people did not consent to the operation, and as a result, these people were under follow-up. The final cohort involved 30 patients with an average age of 55±11 years Surgery group (SG; 20 patients, 2 males and 18 females) and non-surgery group (NSG;10 patients, 3 males and 7 females). 50% of the SG and 80% of the NSG were osteoporotic.

In the surgery group, a significant statistical difference was reported between calcium, phosphorus, PTH and 25(OH) D parameters (p-value of 0.001), with no significant changes in creatinine or albumin. Calcium and PTH levels decreased significantly after two years, although PTH remained elevated in two patients. No significant changes in biochemical parameters were observed in the NSG (Table 2).

Table 1. The laboratory findings in baseline and two years of follow-up.

Parameter	Mean ± SD Baseline		Mean ± SD After two years		P-value (comparison of values before and after separate operation in each group)	
	SG	NSG	SG	NSG	SG	NSG
Calcium	10.8±1	10±0.8	9.5±0.7	9.8±0.5	0.001	0.4
Phosphorus	2.6±0.5	3±0.5	3.5±0.6	3±0.6	0.001	0.8
PTH	149.2±1.87	113±42.6	44.2±21.1	107.6±49.3	0.001	0.7
Vitamin 25(OH)D	25.1±9.6	29.1±8.2	37.6±12.3	39.4±16.2	0.001	0.06
Creatinine	0.8±0.1	0.8±0.07	0.9±0.1	0.9±0.09	0.6	0.3
Albumin	4.6±0.3	4.7±0.2	4.6±0.6	4.7±0.2	0.4	0.8

SG: Surgery Group, NSG: Non-surgery Group

Table 2. The bone densitometry results in patients of the surgery group and the non-surgery group.

Parameter	Mean ± SD Baseline		Mean ± SD After two years		P-value (comparison of values before and after separate operation in each group)	
	SG	NSG	SG	NSG	SG	NSG
Femoral neck Z-score	0.9±1.4	-0.2±1.1	-0.6±1.3	-0.4±1.3	0.06	0.4

Femoral neck T- score	-1.5±1.5	-1.5±1.3	-1.3±1.5	-2.0±1.4	0.09	0.04
Total Spine T- score	-1.9±1.7	-2.4±1.4	-1.5±1.8	-2.7±1.2	0.006	0.2
Total Spine Z- score	-1.09±1.6	-1.5±1.5	-0.6±1.6	-1.9±1.5	0.005	0.1
Distal of radius T- score	3.1±2.7	-4.4±1.05	-2.9±2.3	-4.9±1.04	0.046	0.10
Distal of radius Z- score	-2.4±7.2	-2.9±1.05	-2.0±2.2	-3.3±1.1	0.058	0.10

SG: Surgery Group, NSG: Non-surgery Group

The bone densitometry results including femoral, total spine, and distal of radius T-score and Z-score in the patients of the SG and have been described (Table 3). In the SG, a significant statistical difference was reported between total Spine T and Z score, with a p-value of 0.006 and 0.005, respectively. The results revealed that the bone density of the SG patients in the region of lumbar vertebrae and distal radius has increased significantly after 2 years. (T-score of the distal radius increased significantly in the SG and z-score of the distal radius was on the borderline of significance), also a non-significant increase was seen in the bone density of the femoral neck. In the NSG, there was a significant decrease in the bone density of the patients in the femoral neck region (the T-score of the femoral neck showed a significant decrease and the z-score of the femoral neck showed a non-significant decrease) and in other areas, a non-significant decrease in bone density was observed.

Comparison of BMD changes between the two groups revealed a significant difference only in the change of Z-score at the spine (p=0.02). No other significant differences in BMD changes were observed between the SG and NSG (Table 3).

Table 3. The comparison of bone mineral density (BMD) in two groups and the relationship of initial PTH with the changes.

Parameter	Mean ± SD		P-value (comparison of changes in two groups)	P-value (comparison with initial PTH)
	SG	NSG		
ΔT- Score of femoral neck	-0.2±0.1	-0.3±0.24	0.1	0.1
ΔZ- Score of femoral neck	1.1±4.4	1. 08±1.6	0.7	0.2
ΔT- Score of spine	0.05±0.7	-0.18±0.05	0.7	0.8
ΔZ- Score of spine	-0.06±0.07	-0.5±0.16	0.02	0.3
ΔT- Score of distal radius	-0.9±0.09	-0.13±0.04	0.6	0.5
ΔZ- Score of distal radius	-0.13±0.17	-0.14±0.05	0.4	0.9

SG: Surgery Group, NSG: Non-surgery Group

Discussion

This study demonstrates that parathyroidectomy leads to significant improvements in biochemical parameters and BMD in patients with PHPT. Specifically, we observed significant increases in 25(OH)D and phosphorus, and significant decreases in calcium and PTH in the surgery group. Furthermore, we found significant improvements in BMD at the lumbar spine and distal radius following surgery.

Surgical intervention to correct hypercalcemia and reduce the risk of further complications of hypercalcemia is strongly recommended in younger patients (50 years), those with a history of fracture or osteoporosis, kidney stones, low glomerular filtration rate (<60 mL/min), and hypercalcemia which is more than 1 mg/dL above normal. However, in patients who do not meet these criteria, parathyroidectomy is also offered as a curative treatment option, although the magnitude of the expected benefit in this group of patients is unclear [11]. Agrawal et al. conducted a detailed appraisal of renal manifestations in primary hyperparathyroidism from Indian PHPT registry, before and after curative parathyroidectomy. Their results revealed that PHPT patients with renal manifestations had significantly higher creatinine (109.7 vs 79.6 μmol/L; $P < .0001$) compared to patients without renal manifestations. Parathyroidectomy resolved the clinical symptoms with biochemical cure in the patients from both groups. Patients with renal manifestations showed improvement in creatinine levels after 1 year of curative parathyroidectomy; however, patients without renal manifestations showed no change in creatinine level [12].

Vitamin D deficiency (serum 25(OH)D < 25nmol/L) and insufficiency (serum 25(OH)D between 25 and 30nmol/L) are very common worldwide. Increased catabolism of vitamin D in hyperparathyroidism helps to reduce vitamin D levels. Several studies have shown that patients with higher preoperative PTH level have lower 25(OH)D3, suggesting the coexistence of secondary hyperparathyroidism and a higher prevalence of vitamin D deficiency. A decrease in vitamin D levels after surgery has also been documented in patients with postoperative elevated PTH levels and in patients whose PTH did not eventually return to normal after surgery. These findings support the notion that at least some patients with elevated PTH postoperatively exhibit a mild form of secondary hyperparathyroidism and hypocalcemia due to low vitamin D levels and possibly due to bone remodelling [13].

In the current study, the spine T-Score and Z-Score were significantly changed in the 2-year follow-up. Also, the femoral T-Score was significantly decreased in the NSG. Miguel et al conducted a study that included 32 patients with primary hyperparathyroidism in a single center revealed that the average T-score of the lumbar vertebrae increased significantly after two years [14]. In the present study, the average bone density of the distal radius -although not done in all patients- was lower than that of the femoral neck and lumbar vertebrae and was in the range of osteoporosis [15]. In other words, in hyperparathyroidism, cortical bones such as the forearm are more affected than cancellous bones such as lumbar vertebrae, and the femur bone that is a combination of cortical and cancellous bones, is moderately affected [16]. Lu et al. reported that total hip Z, T score and lumbar spine Z, T score improved after parathyroidectomy. There was a significant increase in the bone density of the lumbar vertebrae and the distal radius, but the increase in the bone density of the femoral neck was not significant [16]. A follow-up study was conducted by Rubin et al. showed that within one year after parathyroidectomy, the bone density of the lumbar vertebrae increases by 8% and the femoral neck increases by 5% [17]. Furthermore, Nordenström et al. studied 126 patients with primary hyperparathyroidism and showed that the lumbar spine and femoral neck had a 12% increase in bone density compared to preoperatively [18].

The correlation between baseline PTH and BMD changes was also investigated, which was not significant. However, some other studies found changes in bone density related to biochemical alterations, which means that patients who had higher PTH and calcium before the operation had more increased bone density in the femur and lumbar vertebrae [19]. Another study revealed that the degree of hypercalcemia is more effective than the PTH level as a surgical benefit [20]. Monique et al. reported a clear improvement in the bone density of patients one year after parathyroidectomy. The highest improvement in bone density was observed in lumbar vertebrae which were 8.6%, followed by femoral neck and total hip, which showed 5.5% improvement. The results obtained from the study were similar to the results of the present study. In addition, forearm bone density also improved in their study, which was also similar to the present study [21]. The changes of biochemical markers of bone formation and resorption such as CTX and PINP after parathyroidectomy were repeatedly investigated in several studies, which are suggested for future studies in our country. In this study, it was mentioned that increased turnover in trabecular bones leads to accelerated recovery of bone density after parathyroidectomy in these areas. It was also mentioned that the rate of metabolism in trabecular bones is 30% and in cortical bones is 3% [21].

Nakaoka et al. showed that patients with primary hyperparathyroidism who were asymptomatic and had no indication for surgery had an increase of 12.2% and 11.6% in lumbar and forearm after parathyroidectomy [22]. Asymptomatic condition has been the main clinical finding in primary hyperparathyroidism in Europe and America in recent years [23]. Even in some developing countries, the changes in clinical symptoms observed at the time of diagnosis vary from asymptomatic to severe symptoms. Many patients with primary hyperparathyroidism are asymptomatic and have mild hypercalcemia, the management of these patients is controversial and overt symptoms are uncommon in the disease [10]. In the current study we excluded 2 patients who received bisphosphonates postoperatively for probable confusing effects. There is a concern about whether combination treatment with bisphosphonates after parathyroidectomy in primary hyperparathyroidism is beneficial or not; Hun Jee Choe et al. in their study declared that there is no additional benefit in prescribing bisphosphonates in PHPT after surgery over parathyroidectomy alone in osteoporotic patients, since combination treatment may interfere with bone mass improvement caused by parathyroidectomy[24].

Limitations

The main limitation of the present study is the small sample size of population. Additionally, the follow-up period of two years may not be sufficient to capture the full extent of BMD changes following surgery. Third, we did not assess changes in bone turnover markers, which could provide additional insights into the mechanisms underlying BMD changes.

Conclusion

Parathyroidectomy significantly improves bone density and biochemical parameters in patients with PHPT, particularly in the lumbar vertebrae and distal radius. These findings support the recommendation of surgery for PHPT patients to prevent osteoporosis and reduce risk of pathological fracture.

Conflict of interest

There is no conflict of interest.

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