Original Article

Changes in bone turnover markers and bone mineral density after radiofrequency ablation for mild primary hyperparathyroidism: a prospective cohort study

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Background: The application of radiofrequency ablation (RFA) is becoming increasingly widespread in the treatment of primary hyperparathyroidism (PHPT). However, the effect of RFA treatment on the skeleton in mild PHPT remains unclear. Therefore, the aim of this study was to investigate the change in bone turnover markers and bone mineral density (BMD) before and 2 years after RFA in patients with mild PHPT.

Methods: In this open-label, prospective study, 81 patients with mild PHPT including 36 treated with RFA and 45 observed without intervention (OBS), along with 81 age-matched healthy controls, were enrolled from November 2018 to September 2021 at Gansu Provincial Hospital. The main outcome measures were levels of serum calcium, serum intact parathyroid hormone (iPTH), and bone turnover markers, including bone-specific alkaline phosphatase (ALP), C-terminal cross-linking telopeptides of type I collagen (β-CTx), and osteocalcin (OC). BMD (femoral neck and lumbar spine) was measured with dual-energy X-ray absorptiometry, and spine radiographs were obtained for vertebral fracture assessment. Paired and unpaired two-tailed *t*-tests and Spearman rank correlation coefficient were used for statistical analyses.

Results: Normalized outcomes for both iPTH and calcium levels were achieved in 32 of 36 (88.9%) patients with mild PHPT treated with RFA. There was a significant treatment effect of RFA on bone turnover biomarkers compared with OBS before the treatment (P=0.04) and at the end of follow-up or (P=0.03). BMD of the lumbar spine increased by 1.8% (P=0.03) and remained stable in the femoral neck (P=0.17) after RFA. However, there was an obvious treatment effect of RFA on BMD compared with OBS (P 0.04). The only compartment with a T-score increase in the RFA group was the lumbar spine in (P<0.001). There was no difference in fracture frequency between groups during the follow-up period.

Conclusions: RFA can improve serum bone turnover markers in patients with mild PHPT and can be expected to increase BMD in the L1–L4 vertebrae and preserve BMD in the femoral neck. Whether RFA can reduce fracture risk in the long-term is a clinical concern for patients with mild PHPT.

Keywords: Primary hyperparathyroidism (PHPT); radiofrequency ablation (RFA); intact parathyroid hormone (iPTH); bone turnover; bone mineral density (BMD)

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Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder typically characterized by elevated serum calcium (sCa) and parathyroid hormone (PTH) levels (1). In 80–85% of cases, PHPT is caused by a single adenoma, but it may also be caused by multiple adenomas, parathyroid hyperplasia, or, very rarely, parathyroid adenocarcinoma (1). Although the disease is frequently associated with bone problems, due to the early detection of a moderate or normal sCa level at the time of biological screening, PHPT is currently more often diagnosed in its mild form (2). Bone involvement, including decreased bone mineral density (BMD) and an increased risk of fractures, has been demonstrated in patients with PHPT, with the overall fracture incidence increasing with age (3). Parathyroidectomy (PTX) is considered the first-line treatment for symptomatic PHPT (4), and its beneficial effect on bone involvement has been extensively demonstrated (5-8). However, some patients may refuse surgery due to unsuitable physical conditions or fear of scar formation and complications from surgery.

Only a limited number of studies have examined the changes in bone turnover markers and BMD improvement in patients with PHPT treated with microwave ablation (MWA) (9,10), and its treatment effect has not yet been fully investigated. In light of this, we conducted an open-label prospective study to evaluate the effects of radiofrequency ablation (RFA) using observations of bone turnover markers and BMD in patients with mild PHPT. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1719/rc).

Methods

Patients

This study was approved by the Ethics Committee of Gansu Provincial Hospital (No. 2021-243) and conducted according to the principles of the Declaration of Helsinki (as revised in 2013). Written informed consent was provided by all participants.

In this open-label prospective study, patients diagnosed with sporadic PHPT in Gansu Provincial Hospital from November 2018 to September 2021 were included, including 36 treated with RFA and 45 who were observed without intervention (OBS). The inclusion criteria were as follows: (I) confirmed diagnosis of asymptomatic PHPT, defined as an elevated serum PTH level with or without elevated blood calcium levels (11,12); (II) at least one enlarged parathyroid gland clearly displayed on ultrasound (US), and (III) positive technetium ^{99m}Tc-sestamibi (MIBI) results or negative MIBI results but with the gland confirmed to be parathyroid tissue by fine-needle aspiration (FNA) and tissue fluid PTH analysis. The patients undergoing RFA were required to meet criteria II and III listed above. All other conditions that could mimic the biochemistry of PHPT were ruled out during the preoperative assessment (13). The flowchart of this study is shown in *Figure 1*.

To compare the bone turnover markers and BMD in patients with PHPT before ablation with those of healthy controls, a group of 81 age and sex-matched healthy controls from the physical examination center of our hospital was created. The patients were divided into two groups: an RFA group and an OBS group.

Preoperative patient evaluation

BMD of the lumbar spine (L1–L4 vertebrae) and left femoral neck was measured with dual-energy X-ray absorptiometry before surgery. Osteoporosis was considered present if a least 1 site had a T-score of less than –2.5. Urolithiasis was recorded with ultrasonography of the abdomen. No patients were treated with osteoporosis medications over the 2 years prior to RFA, no patients were treated with vitamin D before RFA, and there were no recent clinical fractures.

RFA instrument and procedure

US-guided RFA was performed using a LOGIQ E9 system (GE HealthCare, Chicago, IL, USA) with a 6 to 15-MHz linear array probe. A radiofrequency generator (CelonLab POWER, Olympus Surgical Technologies; 18 G × 200-10-30) was used for RFA. The procedure was performed by a single doctor with >12 years of experience in thermal ablation treatment of thyroid and parathyroid nodules. The patient was placed in a supine position with routine disinfection and local anesthesia. Before RFA, contrast-enhanced ultrasound (CEUS) was employed to observe the size and position of the nodules if routine US failed to locate them (*Figure 2A*). Normal saline was continuously injected between the peripheral nodule area and surrounding critical structure (*Figure 2B*) to create a barrier that could prevent thermal injury of adjacent structures. An electrode was inserted

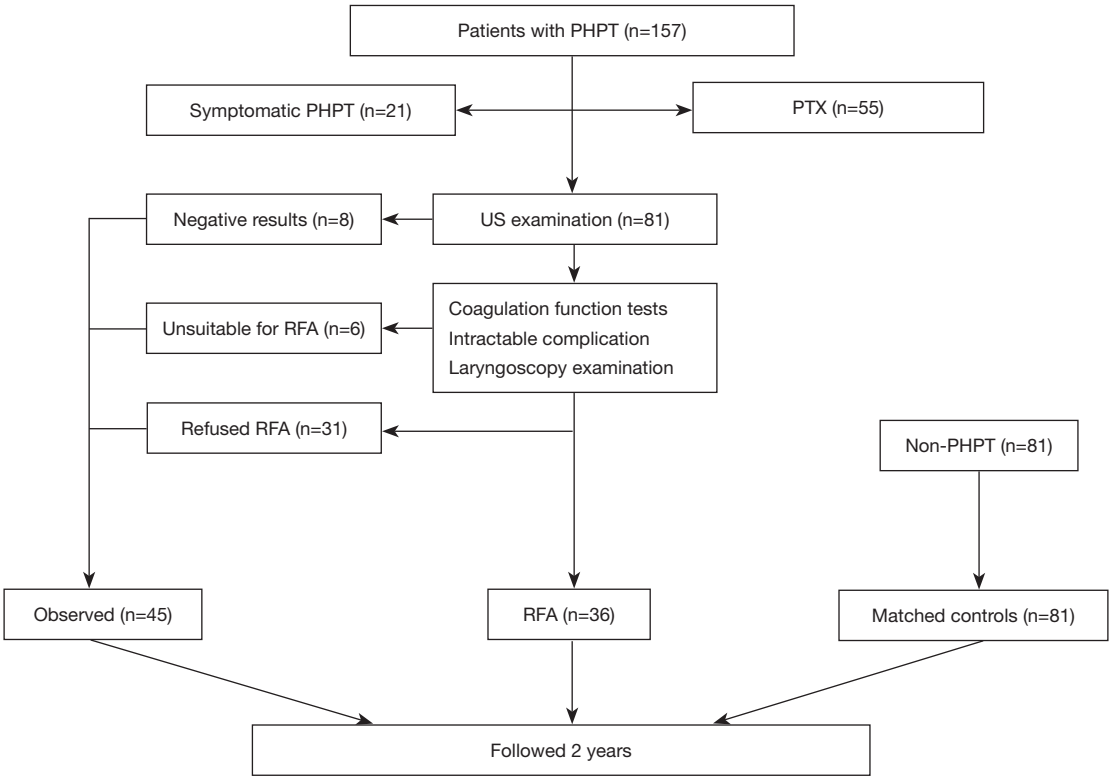

Figure 1 The flowchart of the study. PHPT, primary hyperparathyroidism; PTX, parathyroidectomy; US, ultrasound; RFA, radiofrequency ablation.

and placed into the parathyroid nodule via US guidance, and ablation was performed layer by layer, following the "from far to near" or "from deep to shallow" principle. Ablation of the lesion was covered by the hyperechoic zone (*Figure 2C*). After the ablation, CEUS was performed, in which a lack of enhancement indicated RFA-induced coagulative necrosis (*Figure 2D*). It should be noted that ablation of the contralateral side was only performed when vocal cord movement was normal on US or in patients with bilateral PHPT nodules when there was no voice change after one side was ablated; otherwise, the procedure was stopped, and the second session was suspended until recurrent laryngeal nerve function recovered.

Outcome

The interventions studied were the RFA treatments. The following primary outcome measures were obtained pre- and postoperatively during the follow-up and were compared between the PTX and OBS groups: sCa level; intact parathyroid hormone (iPTH) and bone turnover markers, including bone-specific alkaline phosphatase (ALP), C-terminal cross-linking telopeptides of type I collagen (β-CTx), osteocalcin (OC), and 25-hydroxyvitamin D_3 (25[OH]D_3); and BMD of the lumbar spine (L1–L4 vertebrae) and left femoral neck.

Statistical analysis

SPSS 22.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The normality of the continuous variables was determined via the Shapiro-Wilk test. Normally distributed continuous variables are expressed as the mean ± standard deviation, and skewed distributed continuous variables are expressed as the median with the interquartile range. Paired and unpaired two-tailed *t*-tests and Spearman rank correlation coefficient were used for statistical analyses. The chi-square test was used to compare groups in terms of the development of any new fracture. All statistical tests were two-tailed, with $P<0.05$ being

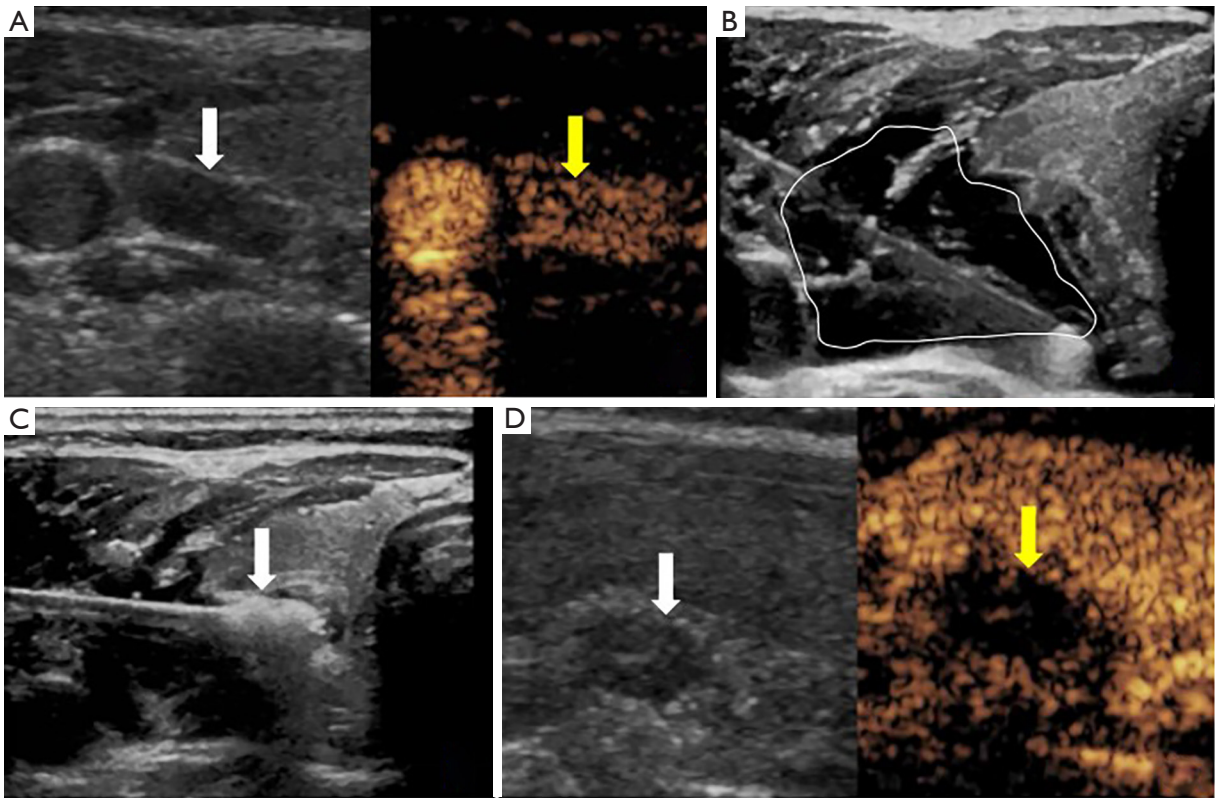

Figure 2 RFA procedure for a parathyroid nodule. (A) Before RFA, traditional ultrasound sonogram revealed hypoechoicity (white arrow), with a regular shape and clear boundary, and uniform and high enhancement in CEUS (yellow arrow). (B) Establishment of hydrodissection (white solid lines). (C) During ablation, the hyperechogenic area represented the ablated area (white arrow). (D) After ablation, the ablated area (white arrow) exhibited no enhancement in CEUS (yellow arrow). RFA, radiofrequency ablation; CEUS, contrast-enhanced ultrasound.

considered statistically significant.

Results

Baseline characteristics

The study enrolled 36 patients with mild PHPT undergoing ultrasound-guided RFA, 45 OBS patients, and 81 controls. The baseline characteristics of the enrolled patients are presented in *Table 1*.

Overall efficacy

Complete ablation was achieved in 36 patients, and the technical success rate was 100%. Follow-up in the surgical cases occurred on average 21 months after RFA. In the follow-up period after RFA, 32 patients had normal levels of serum iPTH and calcium, yielding a cure rate of 88.9% (32/36). All patients tolerated the therapy, with hoarseness being a major complication in 8 patients (13.1%), all of whom achieved complete recovery within 4 months.

In the following 2 years, the levels of serum iPTH and calcium both decreased to the normal reference ranges and tended to be stable in the RFA group, but there was no significant change in the OBS group (*Figure 3*).

Effects on bone metabolic profiles

Patients in the RFA and OBS subgroups had the same biochemical values (*Tables 1*,*2*). ALP correlated negatively with BMD in both the lumbar spine and femoral neck. At follow-up, there was a significant drop in the bone formation (ALP, OC) and resorption (β-CTx) markers in the RFA group compared with the OBS group. The serum ALP level dropped from a mean 122 U/L to a mean 88.5 U/L, corresponding to a 27.5% drop (P=0.005). The OC level dropped by 20.2% from a mean preoperative level

Table 1 The baseline characteristics of all patient cases (n=81), control individuals (n=81), and the treatment subgroups (RFA group: n=36; OBS group: n=45)

Variable	Cases	Controls	P[a]	Subgroup		
				RFA	OBS	P[b]
Mean age (years)	55.1±12.3	56.1±12.3	0.79	51.2±12.4	58.3±17.0	0.04
Weight (kg)	61.7±8.6	60.8±9.4	0.56	61.7±8.7	62.6±10.1	0.66
Height (m)	1.65±0.07	1.64±0.07	0.23	1.65±0.07	1.66±0.08	0.20
BMI (kg/m^2)	22.6±2.8	22.6±3.4	0.72	22.4±2.8	22.3±2.8	0.62
iPTH (pg/mL)	170.1±67.1	47.21±10.2	<0.001	172.9±75.4	157.4±69.5	0.23
Calcium (mmol/L)	2.49±0.22	2.27±0.31	<0.001	2.61±0.27	2.47±0.14	0.04
Urine calcium (mmol/L)	4.71±1.78	2.41±1.01	<0.001	4.98±1.28	4.51±1.18	0.03
eGFR (CKD-EPI) (mL/min)	59.7±12.6	52.5±14.3	0.55	62.3±10.8	61.5±11.4	0.66
25(OH)D_3 (ng/mL)	17.9±6.5	23.4±10.5	0.03	17.9±6.5	18.3±6.1	0.56
ALP (U/L)	122.0±55.4	90.8±24.2	0.006	122.0±55.8	129.9±51.9	0.87
OC (ng/mL)	48.5±19.4	34.4±6.2	0.04	48.5±19.6	46.9±19.4	0.78
β-CTx (ng/mL)	0.66±0.22	0.37±0.08	0.04	0.66±0.22	0.65±0.22	0.66
L1–L4 BMD (g/cm^2)	0.91±0.18	1.07±0.22	0.03	0.92±0.11	0.91±0.21	0.40
T-score	−1.37±1.01	−1.09±0.74	0.007	−1.49±1.12	−1.23±1.08	0.36
Neck BMD (g/cm^2)	0.89±0.24	1.01±0.20	0.04	0.90±0.23	0.92±0.21	0.43
T-score	−1.48±1.23	−1.01±0.88	0.04	−1.55±1.86	−1.38±1.51	0.32

Values are presented as the mean ± SD. [a], paired *t*-test. [b], unpaired *t*-test. RFA, radiofrequency ablation; OBS, observation without intervention; BMI, body mass index; iPTH, intact parathyroid hormone; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; 25(OH)D_3, 25-hydroxyvitamin D_3; ALP, alkaline phosphatase; OC, osteocalcin; β-CTx, C-terminal cross-linking telopeptides of type I collagen; BMD, bone mineral density; SD, standard deviation.

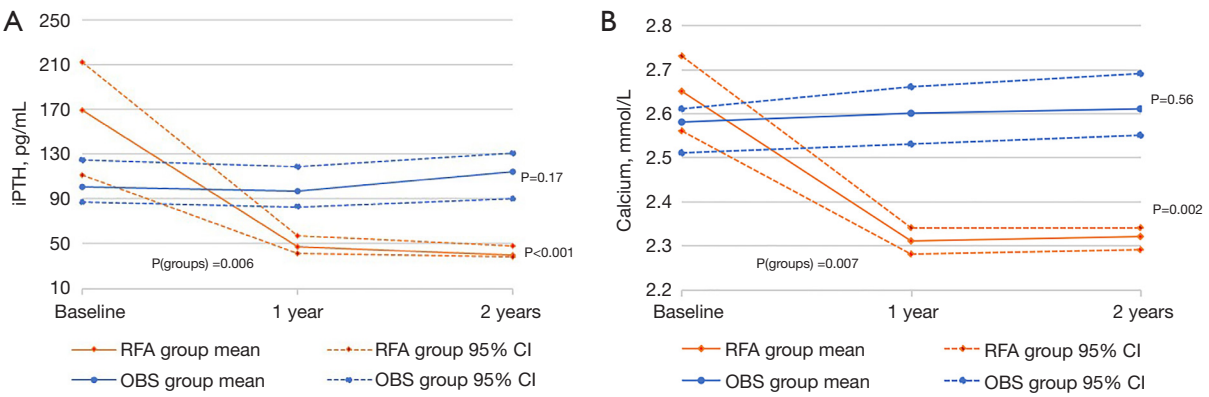

Figure 3 Mean levels with 95% CIs of serum iPTH (A) and calcium (B) in the 2-year follow up for both the RFA and OBS groups. P denotes P value for longitudinal changes within each group. P(groups) denotes the P value for longitudinal changes between groups. iPTH, intact parathyroid hormone; RFA, radiofrequency ablation; OBS, observation without intervention; 95% CI, 95% confidence interval.

Table 2 Bone markers and BMD variables of the RFA and OBS groups at the time of study inclusion and at follow-up

Variable	RFA				OBS				P(groups)
	Inclusion	Follow-up	% change	P	Inclusion	Follow-up	% change	P	
ALP (U/L)	122.0±55.8	88.5±36.5	−27.5	0.005	129.9±51.9	116.1±52.4	−9.4	0.03	0.004
OC (ng/mL)	48.5±19.6	33.7±12.7	−20.2	0.03	46.9±19.4	48.1±6.8	4.1	0.57	0.04
β-CTx (ng/mL)	0.66±0.22	0.48±0.08	−17.1	0.04	0.65±0.22	0.69±0.18	5.2	0.61	0.03
L1–L4 BMD (g/cm^2)	0.91±0.08	1.01±0.19	1.8	0.03	0.91±0.21	0.90±0.17	−2	0.81	0.01
Neck BMD (g/cm^2)	0.82±0.24	0.83±0.25	0.6	0.17	0.92±0.21	0.80±0.19	−11	0.61	0.04

Values are presented as the mean ± SD. P denotes the P value for longitudinal changes from baseline to 2 years within each group according to the paired *t*-test. P(groups) denotes the P value for longitudinal changes between groups from baseline to 2 years. The + or − sign indicates increased or decreased values compared with baseline values, respectively. BMD, bone mineral density; RFA, radiofrequency ablation; OBS, observation without intervention; ALP, alkaline phosphatase; OC, osteocalcin; β-CTx, C-terminal cross-linking telopeptides of type I collagen; SD, standard deviation.

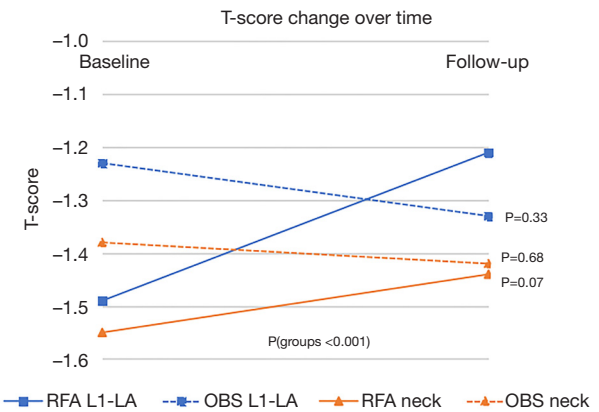

Figure 4 Change in T-scores during the study period at the lumbar spine and femoral neck for both groups. P denotes the P value for longitudinal changes from baseline to 2 years within each group. P(groups) denotes the P value for longitudinal changes between groups from baseline to 2 years. RFA, radiofrequency ablation; OBS, observation without intervention.

of 48.5 ng/mL to a postoperative level of 33.7 ng/mL (P=0.03). The β-CTx level dropped from a mean 0.66 ng/mL to a mean 0.48 ng/mL, corresponding to a 17.1% drop in preoperative values (P=0.04). The BMD of the lumbar spine increased by 1.8% (P=0.03) compared to baseline, the femoral neck BMD increased by 0.6% (P=0.17), and there were no differences in BMD between RFA cases and their matched controls (*Table 2*).

A decrease in T-score was noted for all compartments in the OBS group. The only compartment with a T-score increase in the RFA group was the lumbar spine (P<0.001).

The T-score differences over time for the two groups are illustrated in *Figure 4*.

In the 2-year follow-up, 3 of 45 (6.7%) patients in the OBS group and 2 of 36 (5.6%) patients in the RFA group experienced some type of new fracture (peripheral or vertebral), with no significant difference between groups (P=0.72).

Discussion

This study comprehensively analyzed the bone health and is the first of its kind to compare patients with mild PHPT treated with RFA to those who did not receive any intervention. Bone turnover markers reflect the metabolism of bone cells (osteoblasts, osteoclasts, or osteocytes), and assessment of bone turnover markers helps to assess the status of the skeleton in those with PHPT (14). In our cohort, 81 healthy participants were included as the control group, and the mean baseline values of bone formation markers (ALP, OC), resorption markers (β-CTx), and BMD (femoral neck and lumbar spine) were all elevated or at the upper limit of the normal range, higher than those of controls. This confirms that PTH hypersecretion adversely affects the skeleton. The difference between cases and controls should not be considered fortuitous. The fact that the level of 25(OH)D_3 was considerably low in all patients and in healthy controls is in accordance with a study that reported 25(OH)D_3 insufficiency or deficiency to be common among Chinese adults (15).

In 20 patients with PHPT, Ni *et al.* found bone turnover marker levels to be significantly decreased at 1-year follow-up after MWA (9), indicating a significant MWA treatment

effect compared with that of OBS. In our cohort, reductions in levels of ALP, OC, and β-CTx markers were observed, with a drop of 27.5% for ALP, 20.2% for OC, and 17.1% for β-CTx, which is comparable to the response after PTX (5).

The beneficial effect of PTX on bone involvement has been demonstrated (16-20). In our cohort, as many as 81% of the cases had a low BMD at the lumbar spine or femoral neck compared with 29% of the matched controls, which suggests significant bone loss in patients with mild PHPT. Some researchers have attempted to identify a specific bone marker that can reflect beneficial effects on bone remodeling and microstructure. Ohe *et al.* confirmed that the changes in BMD 1 year after PTX therapy were positively correlated with preoperative biomarkers: the higher the level of preoperative biomarkers, the greater the increase in BMD (20). The measurement of β-CTx may be useful for predicting the long-term changes in lumbar BMD after PTX administration (21). Although our study failed to find a correlation between β-CTx at baseline and BMD changes after RFA, ALP correlated negatively with BMD in both the lumbar spine and femoral neck. There was a decrease of BMD in the lumbar spine of patients with PHPT, which is consistent with other series studies on PTX (5,16-18,22). Another principal finding was that RFA was associated with an increase in the BMD to the level of that of the age-matched controls in the lumbar spine but not in the femoral neck. In another study, recovery was noted in the femoral neck (10). This discrepancy may be explained by the fact the mild or asymptomatic patients in our cohort and the mean age of the included patients with cases were higher, and more than half were postmenopausal women.

In our study, we found no difference in fracture frequency between the RFA and OBS groups during the follow-up period. This may be due to relative short follow-up time of 2 years, during which it might have been difficult to detect any statistically significant fractures. However, a randomized controlled trial, including 191 Scandinavian patients with PHPT, found no between-group differences in fracture frequency over a 10-year follow-up (22). It is thus necessary to determine whether RFA can impede bone remodeling and reduce the risk of fracture frequency by conducting studies with long follow-up periods.

Our study had several limitations that should be addressed. First, as we employed an open-label, prospective design, there was inevitable selection bias due to the groups not being randomized. Second, several parameters were different between the RFA group and OBS group, as those with a higher sCa level were assigned to the RFA group, and milder cases (with a lower sCa level) were assigned to the OBS group, with the latter group tending to be older. Third, as no prior sample size estimation was completed and the sample size was relatively small, our findings may lack sufficient power to draw definite conclusions. Future studies with larger sample sizes and sufficient power are needed to verify the benefits of RFA for bone in patients with mild PHPT.

Conclusions

RFA is a reasonable option in the treatment of mild PHPT. Our findings constitute evidence supporting the short-term benefit of RFA on bone turnover markers and changes in BMD in the lumbar spine.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1719/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1719/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Gansu Provincial Hospital (approval No. 2021-243). Informed consent was provided by all individual participants.

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