Bone 145 (2021) 115871

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Preoperative imaging predicts change in bone mineral density after parathyroidectomy for primary hyperparathyroidism

Gabrielle K. Steinl [a], Randy Yeh [b], Marcella D. Walker [c], Catherine McManus [d], James A. Lee [d], Jennifer H. Kuo [d,*]

[a] Columbia University Vagelos College of Physicians & Surgeons, United States of America
[b] Memorial Sloan Kettering Cancer Center, Department of Radiology, United States of America
[c] Columbia University Irving Medical Center Department of Medicine, Endocrinology, United States of America
[d] Columbia University Irving Medical Center Department of Surgery, Division of GI/Endocrine Surgery, United States of America

ARTICLE INFO

Keywords:
Primary hyperparathyroidism
Parathyroidectomy
Parathyroid adenoma
Parathyroid hyperplasia
Bone density
Bone resorption

ABSTRACT

Background: Bone Mineral Density (BMD) improves after parathyroidectomy (PTX), but data on factors that predict bone recovery are limited. No studies have evaluated if preoperative imaging findings are associated with postoperative change in BMD. We hypothesized that larger, metabolically active glands would be associated with greater increase in BMD after PTX.

Methods: Patients with primary hyperparathyroidism (PHPT) who underwent combined Tc-99m sestamibi and 4D-CT imaging prior to PTX and had pre- and post-operative dual-energy X-ray absorptiometry (DXA) at our institution were considered for inclusion. Retrospectively, data were collected from imaging studies on each parathyroid gland, including estimated weight (using the ellipsoid formula) and contrast enhancement on 4D-CT as well as sestamibi avidity. Total estimated parathyroid weight was calculated. The main outcome measure was the percent change in BMD at the lumbar spine (LS) from pre- to post-operative DXA. Predictors of change in BMD at the LS were assessed.

Results: Complete DXA data was available in 25 patients. Median total parathyroid weight on 4D-CT was 270 mg, and mean change in BMD at the LS was 2.4 ± 4.3%. The increase in BMD was best predicted by higher preoperative serum calcium ($p = 0.01$), greater estimated parathyroid weight ($p = 0.001$), sestamibi avidity ($p = 0.03$), and increased time between DXA scans ($p = 0.03$) in the multivariable model ($R^2 = 0.79$, $p < 0.0001$).

Conclusion: In PHPT, higher preoperative serum calcium, parathyroid gland weight on imaging, and sestamibi avidity are associated with greater increases in BMD after curative PTX. These findings suggest that larger, metabolically active adenomas may mobilize more calcium from bone.

1. Introduction

The majority of patients with primary hyperparathyroidism (PHPT) are asymptomatic, but subclinical skeletal disease including osteoporosis and silent vertebral fractures is not uncommon. Parathyroidectomy (PTX) is recommended in those with osteoporosis, a significant reduction in bone mineral density (BMD), or a vertebral fracture confirmed by imaging [1].

Randomized and observational studies indicate that BMD improves after PTX, but there is substantial inter-individual variability in the skeletal response to surgery [2–12]. The literature has consistently shown that the increase in BMD after surgery is greatest in the lumbar spine (LS), compared to the hip and the radius [2–5,7,9–11]. Few studies have evaluated which patients are most likely to benefit from PTX in terms of BMD gains after surgery. Some data suggest that BMD gains are greatest in premenopausal women [8] and those with the typical biochemical profile (i.e. hypercalcemia and elevated serum parathyroid hormone (PTH) level) [3], as opposed to the normohormonal (hypercalcemia and inappropriately normal (inadequately suppressed) PTH) or normocalcemic (normal serum calcium and elevated PTH) profile.

Elucidating additional factors that predict BMD recovery would allow physicians to better counsel patients as they consider the risks and benefits of PTX. To our knowledge, no studies to date have evaluated whether there is a relationship between preoperative imaging findings,

* Corresponding author at: Herbert Irving Pavilion, 161 Fort Washington Avenue, 8th Floor, Suite 829, New York, NY 10032, United States of America.
E-mail address: jhk2029@cumc.columbia.edu (J.H. Kuo).

https://doi.org/10.1016/j.bone.2021.115871
Received 23 October 2020; Received in revised form 27 January 2021; Accepted 27 January 2021
Available online 2 February 2021
8756-3282/© 2021 Elsevier Inc. All rights reserved.

such as parathyroid gland size and Sestamibi uptake, and postoperative change in BMD. We hypothesized that adenomas that were larger and more metabolically active on preoperative imaging would be associated with greater increases in BMD after PTX.

2. Materials and methods

2.1. Patients and patient data collection

This study was approved by the institutional review board of Columbia University Irving Medical Center. Consecutive patients with PHPT who had combined ^{99m}Technetium sestamibi (MIBI) and parathyroid four-dimensional computed tomography (4D-CT) imaging prior to PTX in the five-year span of August 2013—July 2018 were considered for inclusion. Only patients with both pre- and postoperative DXA scans at our institution were included in order to avoid variability in measurements by different densitometer manufacturers and facilities. Patient data was retrospectively collected from the electronic medical record.

2.2. Diagnosis of primary hyperparathyroidism

All patients with a biochemical diagnosis of PHPT including typical (elevated calcium and PTH), normocalcemic (normal calcium and elevated PTH), and normohormonal PHPT (elevated calcium and normal PTH) were evaluated for possible inclusion in the study. Biochemical data were measured in different clinical labs, all using an intact PTH assay. Normal values were based on the individual laboratory's reference range.

2.3. Preoperative imaging

All patients underwent combined MIBI and 4D-CT in a one-stop imaging protocol for surgical planning, as previously reported [13]. From each imaging report, data were collected on parathyroid glands. Data collected on each gland included estimated weight, presence or absence of Sestamibi tracer uptake, and degree of contrast enhancement in Hounsfield units. Parathyroid gland weights were estimated from the ellipsoid formula using 3-axis measurements from the 4D-CT images. Hounsfield units (HU) were measured by drawing the largest possible circular region of interest (ROI) within the gland, but avoiding the inclusion of nearby structures. Arterial and venous phase enhancement (in HU) was calculated by subtracting the baseline non-contrast HU. Contrast washout was also calculated by subtracting venous phase HU from arterial phase HU. We correlated preoperative imaging findings to the final surgical pathology for each patient. For patients with more than one hypercellular gland on final pathology, weights were added to determine the resected parathyroid weight, HU were averaged, and the binary variable of sestamibi uptake was considered positive if any gland had uptake of the tracer. The total parathyroid weight (of all glands visualized on preoperative imaging) was also calculated.

2.4. Surgical procedures and criteria for cure

Patients diagnosed with PHPT underwent PTX if they were symptomatic (history of nephrolithiasis or fracture) or asymptomatic but met International Workshop Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism [1]. The surgeon determined whether to perform a focused PTX or 4-gland exploration based on preoperative imaging and intraoperative findings. In every operation, intraoperative PTH levels were collected and the operation was complete when the Miami criterion was met (PTH decreased by 50% at 10 min post-excision from the highest value pre-excision) [14]. Patients were deemed cured if they had normalization of serum calcium at 6 months postoperatively. Only cured patients were included in the analysis.

2.5. Bone densitometry

All patients underwent dual energy X-ray absorptiometry (DXA) scanning at CUIMC within the Metabolic Bone Diseases Unit pre- and postoperatively (median time from PTX to post-op DXA = 12 months). Areal BMD was measured at the LS, total hip (TH), femoral neck (FN), and the distal one-third radius using a QDR 4500 instrument (Hologic Inc., Waltham, MA). T- and *Z*-scores were obtained using the manufacturer's reference norms. In vivo precision at this facility is 1.28% at the LS, 1.36% at the TH, and 0.70% for the one-third radius [15]. Bone mineral density (BMD) was measured by an International Society for Clinical Densitometry (ISCD)-certified technician.

2.6. Statistical analysis

Our primary endpoint was the percentage change from pre- to postoperative BMD at the lumbar spine. We evaluated available variables that could be related to bone metabolism based on both pre-existing literature and common clinical knowledge, including age, race, ethnicity, gender, and preoperative biochemical markers (serum calcium, PTH, etc.) as well as the preoperative imaging variables (estimated total parathyroid weight visualized on 4D-CT, contrast enhancement and contrast washout, sestamibi avidity).

Pearson's Correlation and Kendall's Rank Correlation Coefficient were used to evaluate univariate relationships among potential variables as appropriate based on the distribution of the variable. Forward stepwise selection was used to determine the model that accounted for the greatest variability in the outcome measure (i.e. highest adjusted R-squared value). A threshold of $p < 0.25$ was used to select candidates for entry into the multivariable linear regression models [16]. Analyses were conducted with R (R Core Team, 2014) and figures were produced using the package ggplot2 (Wickham, 2009). A two-tailed p-value of <0.05 was considered statistically significant.

3. Results

3.1. Patients

Between August 1, 2013 and July 30, 2018, 684 patients underwent PTX for PHPT at our institution. Of these, 28 had a pre- and postoperative DXA scan both performed at our center (Fig. 1). Patient characteristics are shown in Table 1. Complete DXA data (for all skeletal sites) was available in 25 patients. One patient did not have LS BMD measured due to severe scoliosis, and two patients had only distal one-third radius BMD measured at our institution because other sites had been measured at another institution within the same year. All patients had biochemical confirmation of cure (normalized serum calcium at least 6 months after surgery).

3.2. Change in BMD and preoperative imaging findings

The change in BMD by DXA over time (pre- versus post-operatively) is summarized in Table 2. An increase in BMD was observed in the majority of patients at the LS, FN, and TH, and half of the patients had an increase in BMD at the distal one-third radius. There was a significant increase in the mean BMD at the LS, FN and TH, but not the 1/3 radius (Table 2). There was no significant difference in the change in BMD between males and females ($p = 0.27$) or between single- and multi-gland disease patients ($p = 0.79$). Preoperative imaging findings are summarized in Table 3.

3.3. Univariate analysis of potential predictors of change in BMD

Univariate relationships between potential independent variables and the percent change in BMD at the LS, are depicted in Fig. 2. As shown in Fig. 2, serum pre-operative calcium, arterial phase

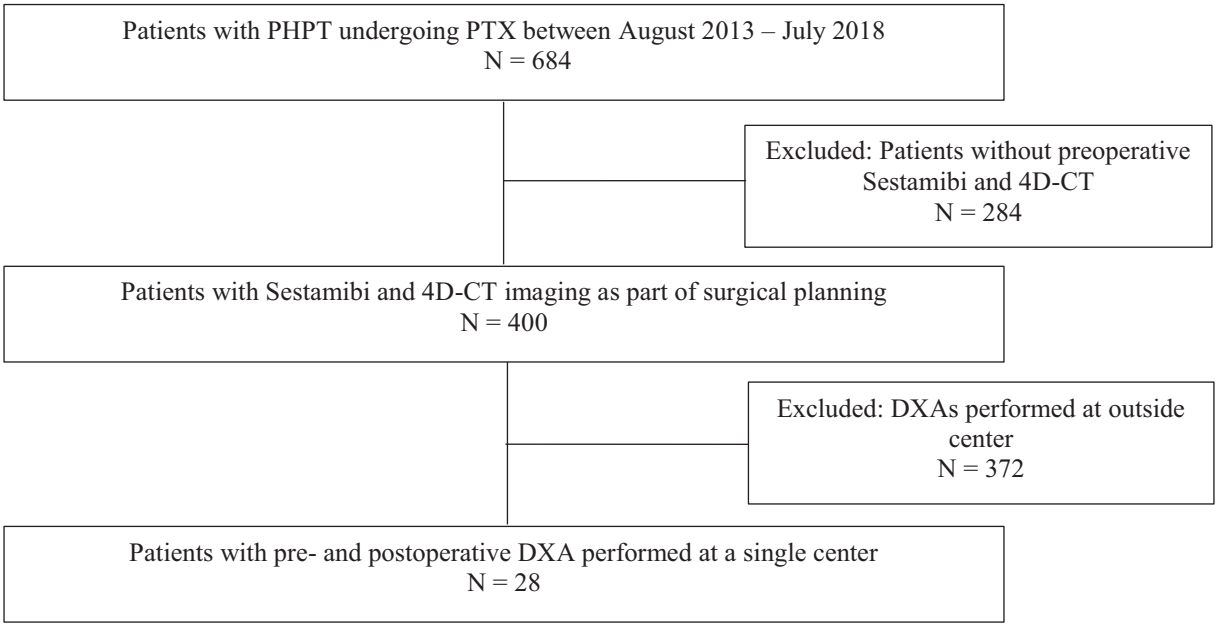

Fig. 1. Patient selection.

enhancement on 4D-CT, total estimated parathyroid weight on imaging, and adenoma uptake of sestamibi were significantly associated with change in BMD at the LS (all $p < 0.05$) post-PTX.

3.4. Multiple regression model to predict change in BMD

Table 4 indicates the step-wise multiple regression model assessing potential predictors of change in BMD at the LS. In the final model, preoperative serum calcium ($p = 0.01$), total parathyroid weight on preoperative 4D-CT ($p = 0.0001$), presence of Sestamibi uptake ($p = 0.03$), and time between pre- and post-operative DXA ($p = 0.03$) were significant independent predictors of the change in BMD at the LS. The final model accounted for 79% of the variability in change in BMD at the LS (adjusted R-squared = 0.79, $p < 0.0001$). The parameter estimates indicate that each 1 mg/dL higher serum calcium pre-operatively was associated with a 2.3% increase in BMD, each additional 100 mg of parathyroid weight was associated with a 0.5% increase in BMD, sestamibi avidity was associated with a 2.2% increase in BMD, and an additional year between pre-and postoperative DXA was associated with a 2.1% increase in BMD. The final model, however, did not predict BMD change at the FN, TH, or distal 1/3 radius (Supp. Table 1). Neither contrast enhancement on arterial phase nor contrast washout (from arterial to venous phase) on 4D-CT were independent predictors of change in BMD.

Because two patients had particularly large adenomas visible on imaging (1540 mg and 2100 mg), we performed a sensitivity analysis, excluding each of these outliers from the model shown in Table 4. Removing either outlier from the sample did not change the relationships in the model significantly; in particular, there was still a significant positive correlation between estimated parathyroid weight and BMD change. Additionally, when we ran our analysis excluding the 9 patients with a history of bisphosphonate treatment, total estimated parathyroid weight on 4D-CT ($p = 0.001$) and serum calcium ($p = 0.02$) were still significant predictors of change in BMD. With the lower sample size, sestamibi avidity and duration between DXA scans were no longer statistically significant predictors.

3.5. Relationship between imaging findings and biochemical data

Finally, we evaluated the relationship of total estimated parathyroid weight on 4D-CT to biochemical indices of disease severity. Parathyroid weight was positively correlated with baseline serum calcium ($r = 0.34$, $p = 0.013$). The associations between weight and serum 25-hydroxyvitamin D ($r = 0.25$, $p = 0.055$) and PTH ($r = -0.26$, $p = 0.066$) were of borderline significance (Supp. Fig. 1).

4. Discussion

In this study, we show that total parathyroid weight estimated by pre-operative 4D-CT and sestamibi avidity predict the increase in BMD at the LS post-PTX in patients with primary hyperparathyroidism. Larger adenomas and sestamibi uptake were associated with greater gains in BMD after surgery. To our knowledge, we are the first to report a relationship between estimated parathyroid weight on preoperative 4D-CT and bone recovery at the LS.

While the relationships between parathyroid weight and sestamibi avidity with BMD change were both statistically significant, the predicted effect on BMD was relatively small (<1% to 2% respectively). This is likely because the average increase in BMD at the LS over the relatively short duration of 16 months pre- to post-PTX was also small (2.4%). It is possible we would have found a larger effect with a study of longer duration. Similar to prior studies, we found the greatest improvement occurred at the LS rather than other skeletal sites, consistent with the greater metabolic activity of cancellous versus cortical bone [2–5,7,9–11]. Despite the relatively small predicted effect on BMD, the results may be helpful to patients with PHPT making decisions about surgery versus observation or in counseling patients preoperatively regarding their anticipated change in BMD after PTX. In particular, patients without tangible symptoms to guide their decision may be hesitant to proceed with an operation, despite randomized, controlled trials demonstrating improvement in BMD, quality of life, and psychological functioning [17–19].

In contrast to our study, Suzuki et al. reported a negative cross-sectional association between the weight of resected parathyroid adenomas at pathology and preoperative BMD. Their results indicate larger adenomas were associated with lower pre-operative BMD [20]. These results, however, are not necessarily inconsistent with our findings since the prior study utilized preoperative BMD, rather than post-operative change in BMD. Greater disease severity (as estimated by gland size) would be expected to be associated with worse skeletal health pre-

Table 1
Patient demographics and preoperative characteristics.[a]

Variable	Whole cohort (n = 28)
Age (years)	60.9 ± 12.4
Sex (% female)	82.1% (23)
BMI	23.1 ± 3.9
Height (inches)	64.2
Weight (pounds)	137.8
Race	
White	75.0% (21)
Black or African American	14.3% (4)
Asian	7.1% (2)
Unknown	3.6% (1)
Ethnicity	
Hispanic or Latino	17.9% (5)
Non-Hispanic or Latino	75.0% (21)
Unknown	7.1% (2)
Biochemical	
Preoperative serum calcium, mg/dL	10.6 ± 0.6
Preoperative PTH, pg/mL	101.4 ± 64.6
Preoperative 25-hydroxyvitamin D, ng/mL	30.1 ± 10.0 (n = 27)
Typical PHPT	60.7% (17)
Normocalcemic PHPT	25.0% (7)
Normohormonal PHPT	14.3% (4)
Multigland disease	35.7% (10)
Bone health	
Osteoporosis	67.9% (19)
Osteopenia	25% (7)
History of bisphosphonate use	32.1% (9)
Duration of therapy, years	5 (1.25–14)
Time between stopping therapy and PTX, years[b]	3 (0–7)
Prior fracture	35.7% (10)
Preoperative T-score	
Lumbar spine	−1.8 ± 1.0 (*n* = 25)
Femoral neck	−2.1 ± 0.9 (*n* = 27)
Total hip	−1.5 ± 1.0 (n = 27)
One-third radius	−1.7 ± 1.5 (*n* = 28)
Time from surgery to postoperative DXA, months	12 (10–13)
Time between pre-and postoperative DXA, months	16 (12–36)
Systemic steroid therapy (%)	7.1% (2)
History of estrogen replacement therapy (%)[c]	28.6% (8)
Taking calcium supplement	25% (7)
Taking vitamin D supplement	67.9% (19)

[a] Data is for the entire cohort (n = 28) unless otherwise specified due to missing data. Data are reported as mean ± SD (n), median (range) or percentage (n).
[b] One patient started bisphosphonate therapy 15 months before PTX and continued treatment between PTX and post-op DXA.
[c] 7 of 8 patients had discontinued estrogen therapy 5 years or more prior to the initial DXA. One patient had been using an estrogen patch for 17 years prior to surgery and continued to use it through the time of postoperative DXA and beyond.

Table 2
Change in bone mineral density after parathyroidectomy.[a]

	Lumbar spine	Femoral neck	Total hip	Distal 1/3 radius
	N = 25	N = 27	N = 27	N = 28
Preoperative BMD (g/cm^2)	0.851 ± 0.104	0.622 ± 0.107	0.762 ± 0.128	0.615 ± 0.098
Postoperative BMD (g/cm^2)	0.868 ± 0.114	0.635 ± 0.110	0.777 ± 0.129	0.6130 ± 0.099
Average change in BMD (g/cm^2)	0.021 ± 0.037	0.011 ± 0.029	0.010 ± 0.022	−0.002 ± 0.016
p-Value	**0.009**	**0.046**	**0.035**	0.846
BMD increased after PTX	76.0% (19)	63.0% (17)	63.0% (17)	50% (14)
Percentage change in BMD	2.4% ± 4.3%	1.7% ± 4.5%	1.3% ± 3.0%	−0.2% ± 2.8%

[a] Data are reported as mean ± SD. BMD = bone mineral density, PTX = parathyroidectomy. *P*-values are based on Wilcoxon Signed-Rank test evaluating the difference between pre- and postoperative BMD (bold = $p < 0.05$).

Table 3
Pre-operative imaging findings on SPECT/CT.[a]

	Patients (*n* = 28)
Initial imaging report consistent with final surgical pathology	75.0% (21)
Estimated weight of pathology-confirmed adenoma(s) (mg)	141 (95–302)
Total estimated parathyroid weight (mg)	270 (130–340)
Arterial phase enhancement of pathology-confirmed adenoma(s) (Hu)	+111 ± 45
Venous phase enhancement of pathology-confirmed adenoma(s) (Hu)	+68 ± 24
Focal increase in sestamibi uptake seen	67.9% (19)

[a] Data are reported as percentage (n), median (IQR), or mean ± SD. One patient had an outlier estimated adenoma weight of 2100 mg, and one patient had an estimated adenoma weight of 1540 mg. Total estimated parathyroid weight = sum of all parathyroid mass visualized on 4D-CT, estimated by the ellipsoid formula. Weight of Adenoma(s) refers to the single adenoma weight in single-gland patients and the cumulative adenoma weights in multi-gland patients. Hu = Hounsfield units.

operatively, but also the greatest gains in BMD after cure of the disorder.

To our knowledge, no other studies have assessed the relationship between sestamibi tracer uptake and change in BMD after PTX. Techtenium-99m-sestamibi is a radioactive tracer which is taken up by cells with a high mitochondria concentration, such as normal myocardium and hypercellular or adenomatous parathyroid glands that are very metabolically active [21]. Previous literature has found positive associations between sestamibi uptake and resected adenoma weight as well as baseline serum calcium [21–23]. Additionally, sestamibi uptake has been found to be negatively correlated with preoperative lumbar spine T-scores, but postoperative change in BMD was not evaluated [24].

A positive association between serum calcium level and improvement in BMD post-PTX is consistent with our prior published work [3]. We previously found that an increase of 1 mg/dL in baseline serum calcium was associated with a 1.0% increase in BMD at the LS one year post-PTX [3]. In our current model, calcium was associated with an increase in BMD at the LS of a similar magnitude. On the other hand, neither baseline PTH nor 25-hydroxyvitamin D were significant predictors of improvement in BMD at the LS in either the current or prior study [3].

The null relationship we observed between contrast attenuation on 4D-CT and change in BMD was not entirely unexpected as Hounsfield units generally measure tissue density and not necessarily biologic activity. However, given that we had 4D-CT data available for each patient and this had never been explored, we felt that it was worth evaluating any potential relationships.

We recognize that baseline serum calcium level and sestamibi avidity may be the only predictor variables the clinician has access to, as 4D-CT imaging may not be readily available. However, even after excluding bisphosphonate-treated patients, calcium was significantly associated with BMD change independent of the estimated parathyroid weight taken from the 4D-CT images. Sestamibi avidity was not statistically significant after excluding these 9 patients, but we suspect this is related to the smaller sample size and that sestamibi avidity may be an independent predictor of BMD change. Our results, if validated, could therefore still be useful to a wide range of clinicians in both community and academic settings.

Additionally, we found that time between pre- and postoperative DXA was a significant independent predictor of change in BMD at the LS. Although all patients had their postoperative DXA between 10 and 13 months after PTX, the time between pre- and postoperative scan ranged from 12 to 36 months. Patients with greater time between scans had greater opportunity for change in BMD after PTX. However, our findings indicating an association of adenoma weight, sestamibi avidity and serum calcium with post-operative changes in BMD at the spine were independent of duration between DXA scans.

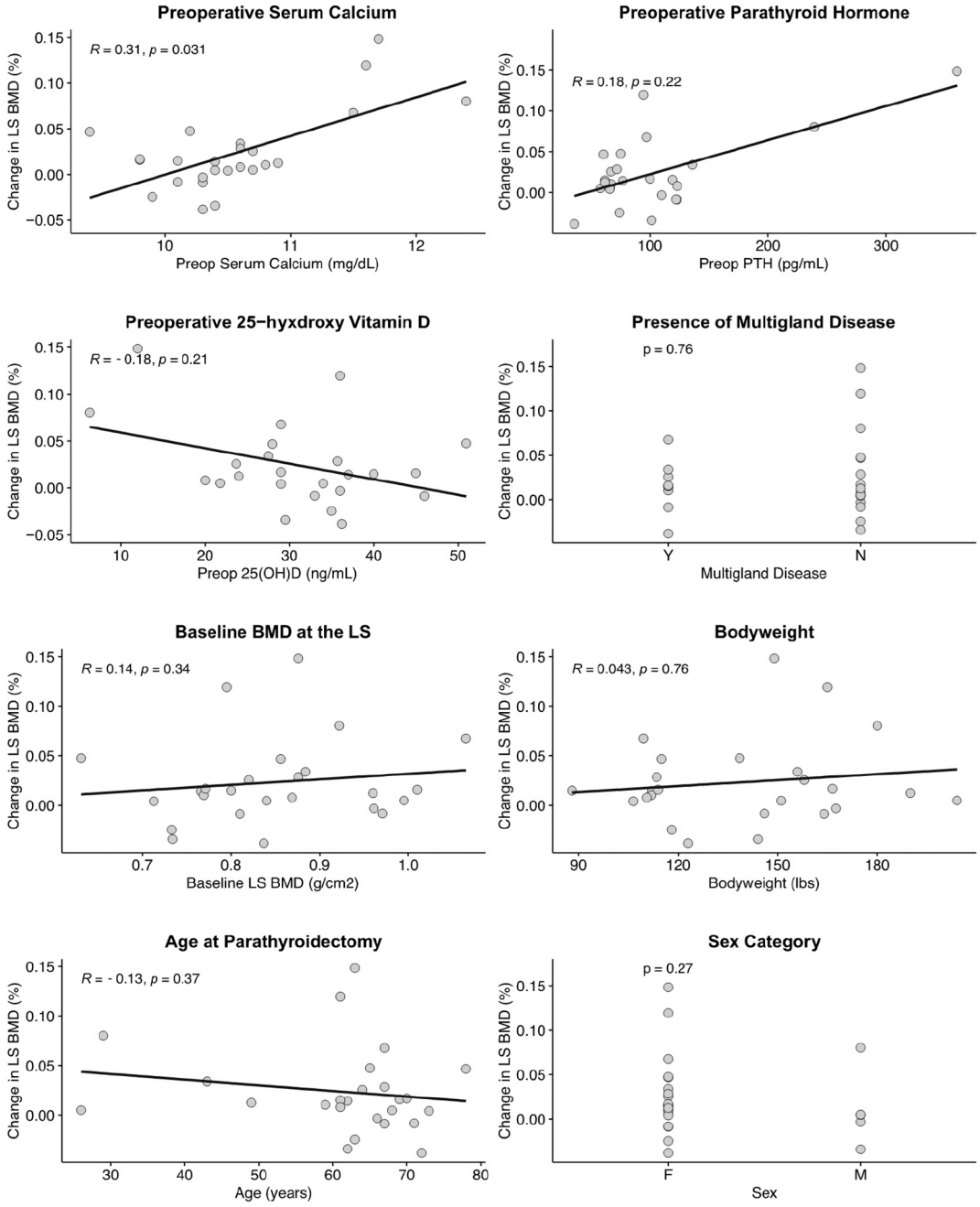

Fig. 2. Univariable analysis: potential predictors of bone recovery at the lumbar spine [1].

Taken together, our findings may suggest that larger, more metabolically active parathyroid adenomas tend to mobilize more calcium from bone. Subsequently, such patients have greater potential for recovery of BMD after a curative PTX. While we cannot infer any causal relationships from this study, we did find that total parathyroid weight estimated on preoperative 4D-CT significantly correlated with baseline serum calcium, which would support this theory.

Our study is not without limitations. First, we must acknowledge our small sample size. Due to the incomparability of BMD across densitometers and centers, we had to limit our sample to those patients who had a DXA at our site. Larger studies will be useful to confirm our findings. Additionally, the prevalence of multiglandular disease (35.7%) is higher than that reported in patients with PHPT (~15–20%) [25]. We suspect patients with multiglandular disease are more likely to be referred to a tertiary center. Thus, our findings may not be generalizable to all patients with PHPT, though we did not find a significant difference in the change in BMD in patients with multi- vs. single-gland disease. We were also not able to evaluate actual resected parathyroid weight because specimen weights are generally recorded to one decimal point in grams, thus there was very limited variability with most specimens being around "0.2 g." Data on alkaline phosphatase levels, a marker of bone disease, were unavailable in this cohort and thus could not be evaluated as a potential predictor variable. Finally, we were interested in evaluating "duration of hyperparathyroidism" as a variable, but given that most patients were referred from other centers and we did not have their complete medical records, it was impossible to estimate when the PHPT started with any accuracy.

Our study also has several strengths. First, we were the first ever

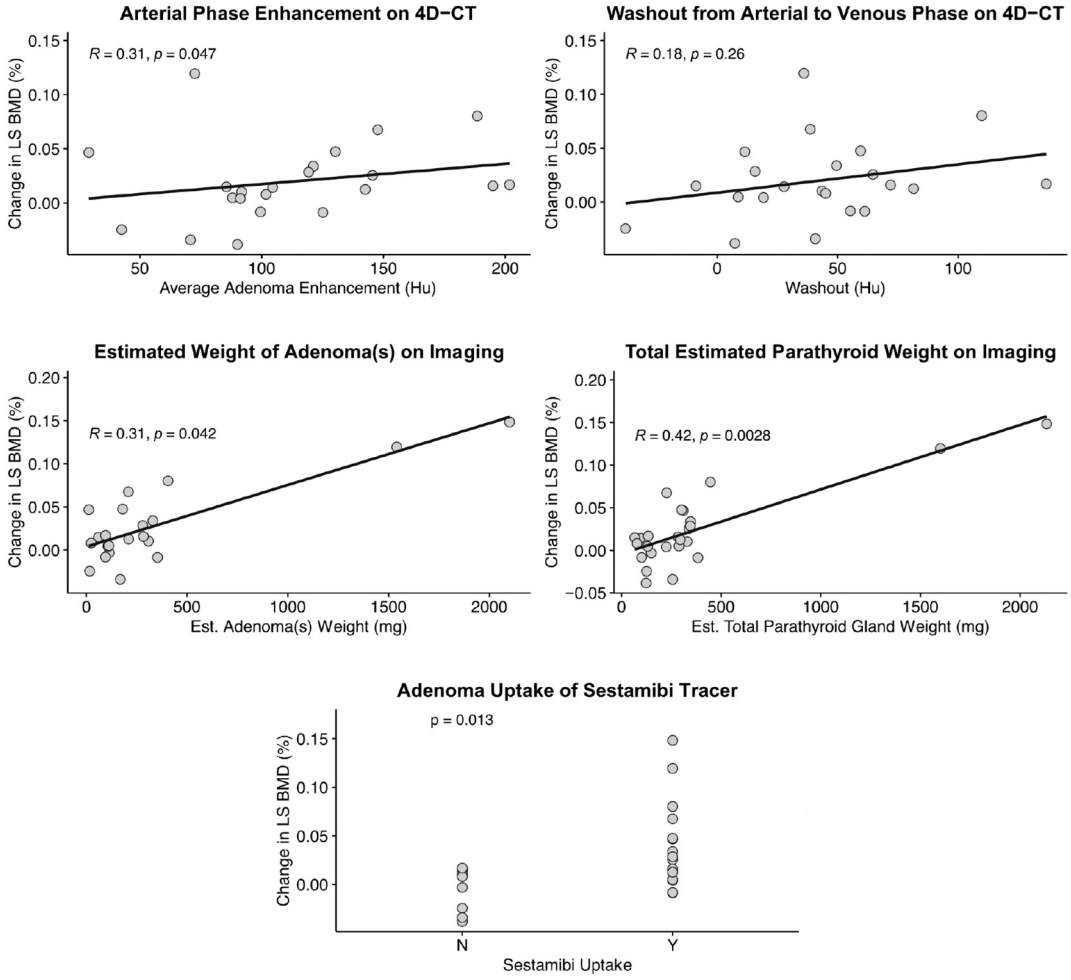

Fig. 2. (*continued*).

Table 4
Multivariable model to predict BMD change at the lumbar spine after parathyroidectomy.[a]

Explanatory variable	Predicted BMD change (β)	95% CI	P-value	Model diagnostics
Preoperative serum calcium (per 1 mg/dL increase)	2.278%	0.602%–3.954%	**0.0102**	Multiple R^2 = 0.82 Adjusted R^2 = 0.79
Total parathyroid weight on CT (per 100 mg increase)	0.522%	0.294%–0.749%	**0.0001**	***p* < 0.0001**
Sestamibi avidity (present)	2.206%	0.305%–4.107%	**0.0251**	
Time from pre- to postoperative DXA (per 1-year increase)	2.072%	0.223%–3.921%	**0.0300**	

Bolded *p*-values <0.05.

[a] CI = confidence interval, BMD = bone mineral density, β = beta coefficient, CT = computed tomography. Parathyroid gland weights were estimated using the ellipsoid formula and added. In patients with multi-gland disease, Sestamibi avidity refers to tracer uptake in any of the glands.

study to evaluate the ability of preoperative imaging variables to predict postoperative DXA changes in PHPT. Our decision to limit our cohort to patients who had both DXA scans performed with a single machine increases the validity of our data, as significant discordance has been found when evaluating BMD change over time using different densitometers [26]. By including patients with both sestamibi and 4D-CT, interpreted by radiologists with significant experience in parathyroid imaging, we were able to evaluate multiple imaging variables. Additionally, we had patients with each of the three biochemical profiles of PHPT (typical, normocalcemic, and normohormonal) which allowed us to again assess and confirm the effect of preoperative serum calcium on predicted change in BMD [3].

5. Conclusions

In summary, greater total parathyroid weight estimated by preoperative 4D-CT and sestamibi avidity on SPECT/CT predict a greater increase in BMD at the lumbar spine post-PTX. We believe that these findings add important insight into factors that influence bone recovery after PTX and may prove helpful when counseling patients regarding potential benefits of PTX.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Gabrielle K. Steinl: Investigation, Formal analysis, Visualization, Writing – original draft. **Randy Yeh:** Resources, Writing – review & editing. **Marcella D. Walker:** Resources, Methodology, Writing –

review & editing, Supervision. **Catherine McManus:** Resources, Supervision. **James A. Lee:** Resources, Supervision. **Jennifer H. Kuo:** Resources, Conceptualization, Methodology, Supervision.

Declaration of competing interest

Dr. Kuo is the recipient of a ThyCa research award from the American Thyroid Association.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2021.115871.

References

[1] J.P. Bilezikian, M.L. Brandi, R. Eastell, et al., Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop, J. Clin. Endocrinol. Metab. 99 (2014) 3561–3569, https://doi.org/10.1210/jc.2014-1413.

[2] G.A. Miguel, F.H. Carranza, J.C.R. Rodriguez, et al., Trabecular bone score, bone mineral density and bone markers in patients with primary hyperparathyroidism 2 years after parathyroidectomy, Horm. Metab. Res. 51 (2019) 186–190, https://doi.org/10.1055/a-0850-8679.

[3] D. Lee, M.D. Walker, H.Y. Chen, J.A. Chabot, J.A. Lee, J.H. Kuo, Bone mineral density changes after parathyroidectomy are dependent on biochemical profile, Surgery 165 (2019) 107–113, https://doi.org/10.1016/j.surg.2018.04.065.

[4] Y.D. Tay, N.E. Cusano, M.R. Rubin, J. Williams, B. Omeragic, J.P. Bilezikian, Trabecular bone score in obese and nonobese subjects with primary hyperparathyroidism before and after parathyroidectomy, J. Clin. Endocrinol. Metab. 103 (2018) 1512–1521, https://doi.org/10.1210/jc.2017-02169.

[5] N.E. Cusano, M.R. Rubin, B.C. Silva, et al., Skeletal microstructure and estimated bone strength improve following parathyroidectomy in primary hyperparathyroidism, J. Clin. Endocrinol. Metab. 103 (2018) 196–205, https://doi.org/10.1210/jc.2017-01932.

[6] P. Rajeev, A. Movseysan, A. Baharani, Changes in bone turnover markers in primary hyperparathyroidism and response to surgery, Ann. R. Coll. Surg. Engl. 99 (2017) 559–562, https://doi.org/10.1308/rcsann.2017.0092.

[7] M.R. Rubin, J.P. Bilezikian, D.J. McMahon, et al., The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years, J. Clin. Endocrinol. Metab. 93 (2008) 3462–3470, https://doi.org/10.1210/jc.2007-1215.

[8] F. Lumachi, V. Camozzi, M. Ermani, F. DEL, G. Luisetto, Bone mineral density improvement after successful parathyroidectomy in pre- and postmenopausal women with primary hyperparathyroidism: a prospective study, Ann. N. Y. Acad. Sci. 1117 (2007) 357–361, https://doi.org/10.1196/annals.1402.012.

[9] E. Nordenstrom, J. Westerdahl, A. Bergenfelz, Recovery of bone mineral density in 126 patients after surgery for primary hyperparathyroidism, World J. Surg. 28 (2004) 502–507, https://doi.org/10.1007/s00268-004-7274-y.

[10] D. Nakaoka, T. Sugimoto, T. Kobayashi, T. Yamaguchi, A. Kobayashi, K. Chihara, Evaluation of changes in bone density and biochemical parameters after parathyroidectomy in primary hyperparathyroidism, Endocr. J. 47 (2000) 231–237, https://doi.org/10.1507/endocrj.47.231.

[11] M. Abdelhadi, J. Nordenstrom, Bone mineral recovery after parathyroidectomy in patients with primary and renal hyperparathyroidism, J. Clin. Endocrinol. Metab. 83 (1998) 3845–3851, https://doi.org/10.1210/jcem.83.11.5249.

[12] L.H. VanderWalde, I.L. Liu, T.X. O'Connell, P.I. Haigh, The effect of parathyroidectomy on bone fracture risk in patients with primary hyperparathyroidism, Arch. Surg. 141 (2006) 885–889, discussion 9-91, https://doi.org/10.1001/archsurg.141.9.885.

[13] R. Yeh, Y.D. Tay, G. Tabacco, et al., Diagnostic performance of 4D CT and Sestamibi SPECT/CT in localizing parathyroid adenomas in primary hyperparathyroidism, Radiology 291 (2019) 469–476, https://doi.org/10.1148/radiol.2019182122.

[14] G.L. Irvin 3rd, D.L. Prudhomme, G.T. Deriso, G. Sfakianakis, S.K. Chandarlapaty, A new approach to parathyroidectomy, Ann. Surg. 219 (1994) 574–579, discussion 9-81, https://doi.org/10.1097/00000658-199405000-00015.

[15] S.L. Bonnick, C.C. Johnston Jr., M. Kleerekoper, et al., Importance of precision in bone density measurements, J. Clin. Densitom. 4 (2001) 105–110, https://doi.org/10.1385/jcd:4:2:105.

[16] Z. Bursac, C.H. Gauss, D.K. Williams, D.W. Hosmer, Purposeful selection of variables in logistic regression, Source Code Biol. Med. 3 (2008) 17, https://doi.org/10.1186/1751-0473-3-17.

[17] E. Ambrogini, F. Cetani, L. Cianferotti, et al., Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial, J. Clin. Endocrinol. Metab. 92 (2007) 3114–3121, https://doi.org/10.1210/jc.2007-0219.

[18] D.S. Rao, E.R. Phillips, G.W. Divine, G.B. Talpos, Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism, J. Clin. Endocrinol. Metab. 89 (2004) 5415–5422, https://doi.org/10.1210/jc.2004-0028.

[19] G.B. Talpos, H.G. Bone 3rd, M. Kleerekoper, et al., Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey, Surgery 128 (2000) 1013–1020, discussion 20-1, https://doi.org/10.1067/msy.2000.110844.

[20] S. Suzuki, T. Fukushima, H. Ami, et al., Pre- and postoperative bone metabolism of primary hyperparathyroidism, Biomed. Pharmacother. (54 Suppl 1) (2000) 90s–96s, https://doi.org/10.1016/s0753-3322(00)80021-9.

[21] N.Y. Mehta, J.M. Ruda, S. Kapadia, P.J. Boyer, C.S. Hollenbeak, B.C. Stack Jr., Relationship of technetium Tc 99m sestamibi scans to histopathological features of hyperfunctioning parathyroid tissue, Arch. Otolaryngol. Head Neck Surg. 131 (2005) 493–498, https://doi.org/10.1001/archotol.131.6.493.

[22] D. Çayir, M. Araz, A. Yalçindağ, E. Çakal, The relationship between semiquantitative parameters derived from technetium-99m metoxyisobutylisonitrile dual-phase parathyroid single-photon emission computed tomography images and disease severity in primary hyperparathyroidism, Nucl. Med. Commun. 39 (2018) 304–311, https://doi.org/10.1097/mnm.0000000000000803.

[23] T.D. Hoang, A.G. Jani, V.Q. Mai, F.O. Tuamokumo, M.K.M. Shakir, Associations of serum ionized calcium, phosphate, and PTH levels with parathyroid scan in primary hyperparathyroidism, Endocr. Pract. 25 (2019) 16–22, https://doi.org/10.4158/ep-2018-0414.

[24] M. Araz, Ç. Soydal, E. Özkan, et al., The efficacy of fluorine-18-choline PET/CT in comparison with 99mTc-MIBI SPECT/CT in the localization of a hyperfunctioning parathyroid gland in primary hyperparathyroidism, Nucl. Med. Commun. 39 (2018) 989–994, https://doi.org/10.1097/mnm.0000000000000899.

[25] M. Barczyński, R. Bränström, G. Dionigi, R. Mihai, Sporadic multiple parathyroid gland disease—a consensus report of the European Society of Endocrine Surgeons (ESES), Langenbeck's Arch. Surg. 400 (2015) 887–905, https://doi.org/10.1007/s00423-015-1348-1.

[26] S.A. Frost, N.D. Nguyen, J.R. Center, J.A. Eisman, T.V. Nguyen, Discordance of longitudinal changes in bone density between densitometers, Bone 41 (2007) 690–697, https://doi.org/10.1016/j.bone.2007.07.002.