



ORIGINAL RESEARCH

High parathyroid hormone levels after parathyroidectomy for parathyroid adenoma are not related to the cellularity of the remaining glands

Rotem Sagiv MD¹  | Bertha Delgado MD² | Re'em Sadeh MD³ |
Sagi Shashar MD³ | Merav Fraenkel MD⁴ | Ksenia M. Yegodayev MSc⁵ |
Moshe Elkabets PhD⁵ | Ben-Zion Joshua MD, MBA⁶ 

¹Joyce & Irving Goldman Medical School,
Faculty of Health Sciences, Ben-Gurion
University of the Negev, Beer-Sheva, Israel

²Pathology Unit, Soroka University Medical
Center, Beer-Sheva, Israel

³Clinical Research Center of Soroka Medical
Center, Beer-Sheva, Israel

⁴Endocrinology Unit, Soroka University
Medical Center, Beer-Sheva, Israel

⁵Shraga Segal Department of Microbiology,
Immunology, and Genetics, Faculty of Health
Sciences, Ben-Gurion University of the Negev,
Beer-Sheva, Israel

⁶Department of Otorhinolaryngology – Head
and Neck Surgery, Barzilai Medical Center,
Ashkelon, Israel

Correspondence

Ben-Zion Joshua, Department of
Otorhinolaryngology – Head and Neck
Surgery, Barzilai Medical Center, Ashkelon,
Israel.
Email: benzionj@bmc.gov.il

Abstract

Background: Patients with primary hyperparathyroidism (PHPT) treated surgically occasionally have normalized calcium, but persistently high parathyroid hormone (PTH). We hypothesized that a possible explanation for this phenomenon is an underlying hyperplasia rather than adenoma.

Methods: Retrospective cohort of patients who underwent parathyroidectomy for PHPT with biopsy of a normal-appearing parathyroid gland were included. Cellularity level of each biopsy and of the adenoma's rim was determined.

Results: Forty-seven patients were included. Of them, 19 (40%) had postoperative normocalcemia but elevated PTH. There was no correlation between cellularity either in the rim or of the normal-appearing parathyroid gland and postoperative PTH. The postoperative high PTH group had higher preoperative PTH ($P = 0.001$) and larger adenomas ($P = 0.025$).

Conclusions: High PTH levels after successful parathyroidectomy in patients with primary hyperparathyroidism do not appear to result from underlying hyperplasia. A possible alternative explanation is that these patients have a higher preoperative burden of disease.

KEYWORDS

cellularity, elevated PTH levels, parathyroid adenoma, parathyroid hyperplasia, parathyroidectomy

1 | INTRODUCTION

Primary hyperparathyroidism (PHPT) is diagnosed by an elevated parathyroid hormone (PTH) concentration in patients with hypercalcemia and hypercalciuria. Its most common clinical presentation is asymptomatic hypercalcemia.¹ It is recommended that patients with

symptomatic PHPT (nephrolithiasis, symptomatic hypercalcemia) have parathyroid surgery, which is the only definitive therapy.^{2,3} In some patients with asymptomatic disease, surgery is not mandatory. However, this is disputed as some claim that a truly asymptomatic PHPT patient is quite rare.⁴ Whereas most asymptomatic patients do not exhibit disease progression, as defined by worsening hypercalcemia,

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Laryngoscope Investigative Otolaryngology* published by Wiley Periodicals LLC on behalf of The Triological Society.

hypercalciuria, bone disease, and/or nephrolithiasis,⁵ some individuals do progress and would benefit from surgery.^{6,7}

Single adenomas account for up to 80 to 85% of cases of primary hyperparathyroidism.^{8,9} They are usually encapsulated, and 50% are surrounded by normal parathyroid tissue.¹⁰ The resultant hyperparathyroidism is characterized by abnormal regulation of PTH secretion by calcium. However, the secretion in this condition is not completely autonomous and can usually be partially inhibited by a further rise in serum calcium.¹¹

Parathyroid hormone may remain elevated in patients who are cured, achieving eucalcemia after parathyroidectomy of the enlarged gland. This phenomenon occurs in 8 to 40% of patients after curative parathyroidectomy¹² and may not indicate operative failure.¹³

The significance of elevated PTH postoperatively is not yet fully understood. It can be due to a vitamin D deficiency, hungry bone syndrome, inadequate calcium intake, vitamin D end-organ resistance, renal insufficiency with impaired vitamin D activation, primary hypercalciuria, or hypercalciuria due to the use of loop diuretics such as furosemide.¹⁴

We observed that in some patients who underwent successful parathyroidectomy (=postoperative eucalcemia) and a biopsy from a normal-appearing parathyroid gland during surgery, the final pathology was that this healthy-appearing parathyroid sample was hypercellular. Thus, we hypothesized that inadequate reduction of PTH levels after a successful parathyroidectomy of adenoma may be due to hypercellularity (=hyperplasia) of the remaining healthy parathyroid glands. Parathyroid hyperplasia is defined microscopically as a hypercellular lesion, with a heterogeneous population of proliferating cells and a reduction of stromal adipocytes. As opposed to parathyroid adenoma, which is characterized by a lesion confined to a single gland, hyperplasia usually involves more than one gland.¹⁵ In this study, our aim was to investigate the association of elevated PTH after a successful excision of parathyroid adenoma and hypercellularity of the remaining glands.

2 | MATERIALS AND METHODS

2.1 | Study design

Our study conforms to recognized standards according to the Declaration of Helsinki, was approved by the Soroka University Medical Center Biomedical Ethics Committee (Study number 0016-18-SOR), and was a single-center investigator-initiated retrospective cohort study. We were exempted from informed consent according to the protocol because the study was retrospective.

The study population comprised patients who had undergone parathyroidectomy D/T PHPT at the Department of Otolaryngology – Head and Neck Surgery at Soroka Medical Center between the years 2008 and 2018. We included men and women >18 years old who had undergone successful parathyroidectomy of their adenoma and had, in addition, a histologic biopsy evaluation taken from a healthy-appearing gland during the surgery. For the surgery to be considered

successful, their calcium level had to be below the upper level of normal laboratory levels (lower than 10.5 mg/dL) from 1 week after surgery (occasionally it takes a few days for the calcium to drop) and for at least 2 years postsurgery. An immediate postoperative drop in PTH and a histopathological confirmation of a hypercellularity of the suspected gland are also necessary. Patients were categorized according to postsurgical PTH levels: those with lower PTH levels postsurgery than before surgery, but still above the upper level of normal (>72 pg/mL) were compared with patients with normalized PTH levels (<72 pg/mL) after surgery.

Prior to surgery, patients with PHPT underwent adenoma localization using both ultrasound and Technetium (99mTc) sestamibi. If in both modalities, results were concordant, then surgery was directed only to that side; otherwise, four gland exploration was performed. Our routine was that during surgery the enlarged parathyroid was identified, and a search was performed to assess another parathyroid gland on the same side to confirm an adenoma as opposed to hyperplasia. The enlarged parathyroid was sent for frozen sectioning for confirmation. If the second parathyroid was also enlarged, then a formal four gland exploration was performed to assess hyperplasia rather than a single adenoma. However, if the second parathyroid appeared normal, then an incisional biopsy from the normal-appearing parathyroid was obtained. In most cases, an intraoperative PTH (IoPTH) assay was performed.

2.2 | Data collected

Using a computerized database network from Soroka Medical Center, we collected patients' data. Demographic data included age at the time of surgery, gender, and ethnicity. Clinical data included chronic diagnoses and medications, all available results of PTH, calcium, phosphorus, albumin, vitamin D, creatinine, and alkaline phosphatase levels taken both before and after surgery. When more than one test was available, we used the mean value of all tests of the specific period. IoPTH measurements are lacking in the data collected for most of the patients, thus are not included in the analysis. Medical imaging data included the size of the enlarged gland via ultrasound, as measured by the radiologist performing the scan and the Tc (99mTc) sestamibi result (positive or negative) were collected when available. Hospitalization data included date of admission, date of surgery, details about the procedure, and outcomes. Finally, histological findings of the parathyroid adenoma and of the normal-appearing parathyroid gland, size and weight of the parathyroid adenoma, and pathological reports with diagnosis.

A senior pathologist (BD) examined each biopsy slide of healthy parathyroid glands. Then she ranked each biopsy according to its level of cellularity (%), assessed from hematoxylin and eosin-stained tissue sections as the ratio of parathyroid cells compared to the whole tissue, including fat cells and stroma, a standard practice in pathology.^{16,17} We also examined the parathyroid tissue surrounding the adenoma and ranked its cellularity similarly. The level of cellularity relates to the relative percentage of parathyroid cells in the sample,

such that the more parathyroid cells there are in the biopsy, the more cellular the biopsy is defined. The cut-off for hyper cellularity was defined as >50%. Hypercellular normal-appearing glands did not change the intraoperative decision making or the further management, as this is not an accepted approach and there is no supporting evidence for it in the literature.

2.3 | Statistical analysis

Due to the change in PTH levels with the progression of time postsurgery, we examined the population during four time periods: 1 week to 2 months, 2 months to 6 months, 6 months to 2 years, and over 2 years after surgery. Mean PTH levels were calculated at all times when available beginning 1 week postsurgery. Lab results were calculated as the mean level of all available results in the specified time period. Continuous variables were presented as the median [interquartile range (IQR)], and categorical variables were presented as the frequency and percentages. In a univariate analysis, we compared demographic and clinical characteristics between the two groups of the study for normal and high PTH postsurgery. For our primary outcome (cellularity of the adenoma and around the adenoma) and for other continuous variables, we used a Mann-Whitney test. Categorical variables were compared with a chi-square or Fisher's exact test.

To illustrate the association between weight and size of the parathyroid gland and PTH levels, a graph stratified by time periods is presented. Furthermore, to illustrate the association between mean PTH levels and high/low cellularity (cut-off defined as 50%), we present a box plot.

All *P*-values are based on a 2-tailed test of significance, with a *P*-value < 0.05 considered as significant. All statistical analyses were conducted using SPSS version 2.5 (SPSS Inc., Chicago, IL).

3 | RESULTS

Between 2008 and 2018, 289 patients underwent parathyroidectomy. Of them, 77 had more than one parathyroid excised or biopsied. Nineteen were excluded from the study because of multiglandular disease, as observed either before or during surgery; six were excluded because of secondary hyperparathyroidism; and three were excluded because the samples were not taken from the same surgery, but from different surgeries. Moreover, one patient was excluded because the adenoma or hypercellular gland was not found in the histological evaluation and another because of surgical failure (persistent hypercalcemia postsurgery). Hence, the study included 47 patients (demographics and lab results are shown in Table 1) who underwent parathyroidectomy due to parathyroid adenoma, confirmed by pathological diagnosis, and who had had a biopsy of at least one additional parathyroid gland. Of them, for 28 patients a nonadenomatous rim of parathyroid tissue was identified. As seen in Table 1, the median cellularity of both the

TABLE 1 Characteristics of the study population

Demographic characteristics	
Age, median (IQR), years	55 (45, 61)
Gender, N male %	12 (25.5%)
Ethnicity, N Jewish %	38 (80.9%)
Clinical characteristics	
PTH before surgery, median (IQR), pg/mL	231 (115, 257)
Ca before surgery, median (IQR), mg/dL	11.21 (10.7, 11.7)
P before surgery, median (IQR), mg/dL	2.78 (2.47, 3.1)
Vitamin D before surgery, median (IQR), nmol/L	54.5 (41.2, 70)
PTH mean after surgery, median (IQR), pg/mL	59.47 (42.6, 81.5)
Ca mean after surgery, median (IQR), mg/dL	9.45 (9.24, 9.62)
P mean after surgery, median (IQR), mg/dL	3.65 (3.25, 3.92)
Vitamin D mean after surgery, median (IQR), nmol/L	60 (48.13, 72.8)
Size of enlarged parathyroid by US, median (IQR), mm	12 (9, 17)
Tc sestamibi, N positive, %	33 (70.2%)
Cellularity of normal-appearing parathyroid, median (IQR), %	60 (50, 70)
Cellularity around adenoma, median (IQR), %	60 (50, 70)
Size of enlarged parathyroid sample on pathology, median (IQR), cm	1.5 (1, 2)
Weight of enlarged parathyroid sample on pathology, median (IQR), g	0.6 (0.4, 1.33)
Albumin, median (IQR), g/dL	3.9 (3.6, 4.3)

Abbreviation: IQR, interquartile range.

normal-appearing parathyroid gland and of the normal parathyroid rim surrounding the adenoma was 60% (IQR 50, 70). However, interestingly there was no correlation between the cellularity of the parathyroid rim and of the normal-appearing gland (Spearman correlation $R_s = 0.13$, $P = 0.49$).

Tables 2 and 3 and S1-S4, Supporting Information show comparisons of the different parameters between high and low PTH, as measured during the specified time frame after surgery.

Tables 2 and 3 show a division of all 47 patients according to their average PTH level in the period beginning 1 week after surgery, with 19 patients having high mean PTH. When comparing high to low PTH at different time frames after surgery, the only consistent significant association found was that patients with high postoperative PTH, had larger adenomas (measured by the pathologist) and a higher preoperative PTH. Similarly, there was no correlation between the cellularity level of the nonadenomatous rim of the parathyroid adenoma and the postoperative PTH levels (Table S5). Figure 1 shows no difference of mean PTH levels after surgery in low vs high cellularity levels of the biopsied gland. A difference in the size of parathyroid adenoma by

TABLE 2 Comparison of demographic characteristics of patients with normal mean PTH versus high mean PTH 1 week and further on from surgery

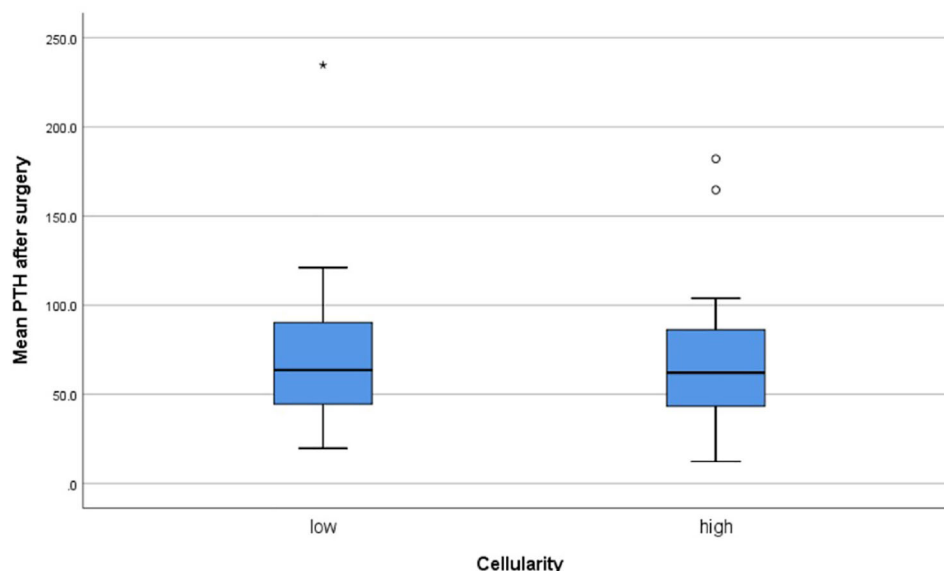
	Normal PTH N = 28	High PTH N = 19	P-value
Age, median (IQR), years	55.5 (45.7, 65.5)	54 (42, 61)	0.37
Gender, N male (%)	8 (28.6%)	4 (21.1%)	0.73
Ethnicity, N Jewish (%)	24 (85.7%)	14 (73.7%)	0.45

Abbreviation: IQR, interquartile range.

TABLE 3 Comparison of clinical characteristics of patients with normal mean PTH versus high mean PTH 1 week and further on from surgery

	Normal PTH N = 28	High PTH N = 19	P-value
Cellularity of normal-appearing parathyroid, median (IQR), %	60 (50, 70)	60 (50, 75)	0.45
Cellularity around adenoma, median (IQR), %	60 (50, 70)	65 (60, 70)	0.25
Size of parathyroid by US, median (IQR), mm	12 (7.6, 15.7)	12 (10, 23)	0.4
Size of parathyroid in pathology, median (IQR), cm	1.4 (1, 1.6)	1.9 (1.4, 3)	0.025
Tc sestamibi, N positive (%)	17 (60.7%)	16 (84.2%)	0.11
Weight of parathyroid, median (IQR), g	0.5 (0.3, 1.1)	0.8 (0.6, 2.3)	0.065
Albumin at surgery, median (IQR), gr/dL	3.9 (3.6, 4.3)	3.9 (3.6, 4.2)	0.72
PTH before surgery, median (IQR), pg/mL	133 (90, 210)	223 (189, 336)	0.001
Mean vitamin D level one week and onward from surgery, N low (<50 nmol/L, %)	9 (37.5%)	4 (23.5%)	0.49
Mean Ca level 1 week and onward from surgery, N low\normal (%)	28 (100%)	19 (100%)	
Mean P level 1 week and onward from surgery, N-Normal (%)	27 (100%)	18 (94.7%)	0.41

Abbreviation: IQR, interquartile range.

FIGURE 1 Mean PTH (pg/mL) postsurgery in low (<50%) versus high (>50%) cellularity level of apparently normal parathyroid biopsies

ultrasound; Tc sestamibi result; or mean vitamin D, calcium, and phosphorus levels was not found between the postoperative high and normal PTH levels. In addition, a difference in demographic characteristics (age, gender, ethnicity) between the high and normal postoperative PTH was also disproven (Tables 2 and S1-S4 and Figures S1 and S2).

A correlation between age and cellularity of the biopsied glands was also ruled out ($R_s = -0.159$, $P\text{-value} = 0.28$).

This study included 12 men and 35 women. When comparing gender, there was no difference in any clinical characteristic except for higher weight of adenomas in the male population

(1.7 [IQR 0.65, 2.1] vs 0.6 [IQR 0.3, 1.05] g, respectively, P -value = 0.014; Table S6).

Following are examples of three patients, including brief demographic and clinical information. Each of them had a different cellularity level of the apparently normal parathyroid gland as demonstrated in the histologic slides below.

Patient A, a 56-year-old female of Jewish origin, had a parathyroidectomy in 2015 due to osteoporosis and symptoms of leg pain, polyuria, and polydipsia. Before surgery, the size of the enlarged parathyroid was evaluated by ultrasound to be 9 mm, and the Tc sestamibi result was negative. During surgery, a 10-mm, 0.2 g parathyroid gland was excised. The patient's calcium level decreased from 11.7 mg/dL before surgery to 10 mg/dL a month postsurgery and remained in the normal range (defined as 8.5-10.5 mg/dL) during 2 years of follow-up. Her phosphorus level increased from 2.9 mg/dL before surgery to 4.1 mg/dL in the following month and continued to be normal thereafter. Vitamin D level (normal range defined as 50-100 nmol/L) was 79 nmol/L 3 months before surgery and 101 nmol/L a year-and-a-half post-surgery. PTH level (normal range defined as 14-72 pg/mL) normalized from 172.2 pg/mL 3 months before surgery to 45.3 pg/mL a month later and remained in the normal range during 2 years of follow-up. In a biopsy of other apparently normal glands, we estimated the cellularity level as 70%, meaning it was hypercellular

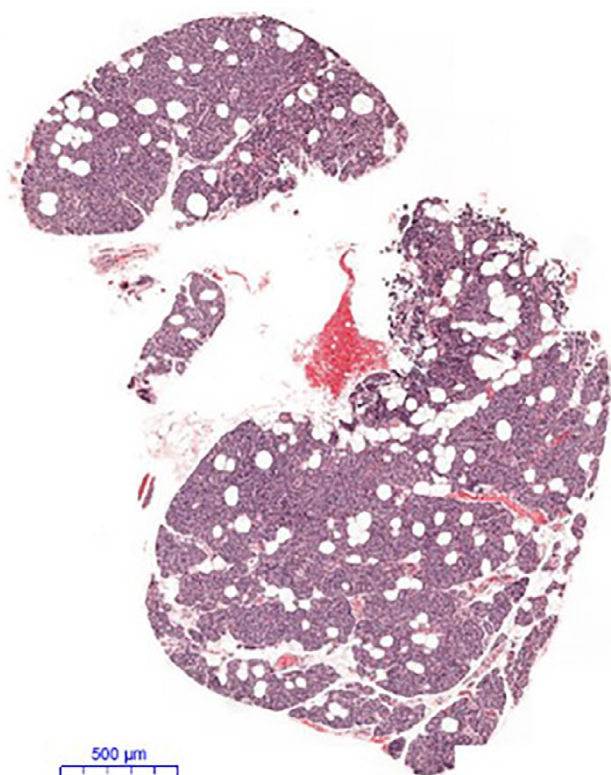


FIGURE 2 Patient A (see text): Parathyroid tissue from an incisional biopsy of a normal-appearing parathyroid showing parathyroid tissue with mild hyper cellularity of ~70%. Hematoxylin-eosin stain, original magnification $\times 20$

(see Figure 2). The cellularity level of the parathyroid tissue surrounding the adenoma was also estimated as 70%.

Patient B, a 49-year-old female of Bedouin origin, had a parathyroidectomy in 2015 due to osteoporosis and symptoms of tiredness, bone pain, and polyuria. Before surgery, the size of the enlarged parathyroid was evaluated by ultrasound to be 25 mm, and the Tc sestamibi result was negative. During surgery, a 30-mm, 1.8 g parathyroid gland was excised. The patient's calcium level decreased from 11.1 mg/dL before surgery to 8.2 mg/dL a month later and remained in the normal range for a year-and-a-half of follow-up. Her phosphorus level was 2.6 mg/dL before surgery, increasing to 3.3 mg/dL in the next month and remaining elevated for a year-and-a-half of follow-up. Her vitamin D level was 44 nmol/L, a month before surgery, 63 nmol/L 4 months after surgery, and decreased after 3 years of follow-up. PTH level decreased from 257.8 pg/mL a month before surgery to 78.2 pg/mL a month later, and returned to a normal range after 3 years of follow-up. In a biopsy of other apparently normal glands, we estimated the cellularity level as 40%, meaning hypocellularity (see Figure 3). The cellularity level of the parathyroid tissue surrounding the adenoma was estimated as 30%.

Patient C, a 49-year-old male of Bedouin origin, had a parathyroidectomy in 2016. He was asymptomatic, and the indication for surgery was his age (<50 years). Before surgery, the size of his enlarged parathyroid was evaluated by ultrasound to be 10 mm, and the Tc sestamibi result was positive. During surgery, a 15 mm, 0.8 g parathyroid gland was excised. The patient's calcium level decreased from 11.9 mg/dL a month before surgery to 9.6 mg/dL 2 weeks afterward, and remained normal in more than 2 years of follow-up. His phosphorus level increased from 3.5 mg/dL a month prior to

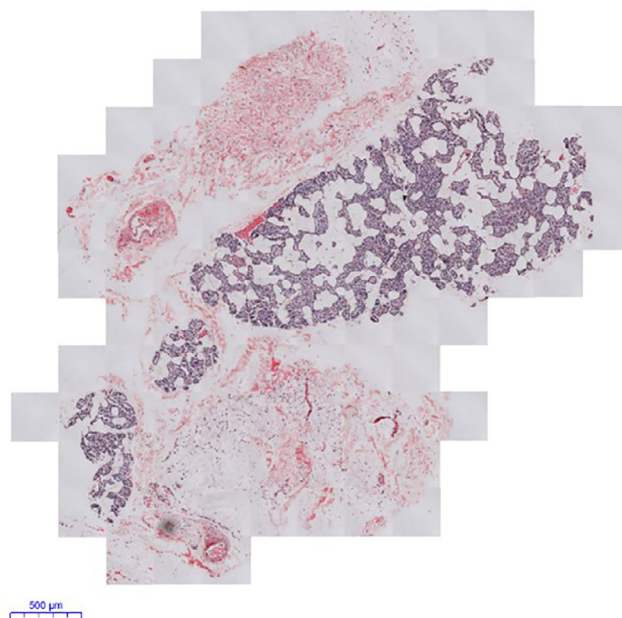


FIGURE 3 Patient B (see text): Parathyroid tissue from an incisional biopsy of a normal-appearing parathyroid showing parathyroid tissue with mild hypocellularity of ~40%. Hematoxylin-eosin stain, original magnification $\times 20$

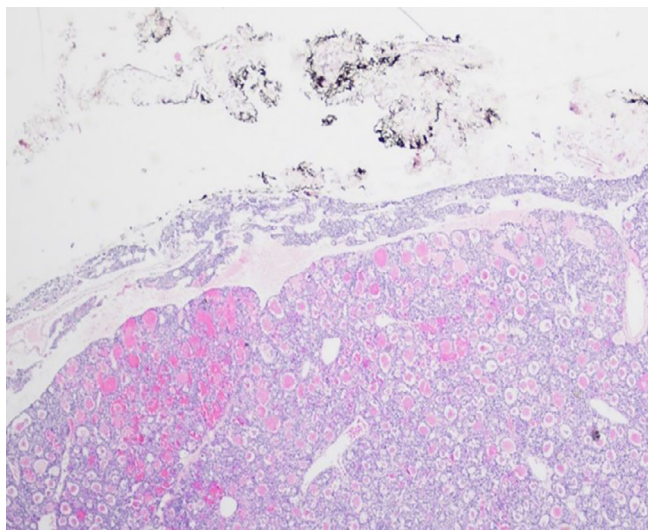


FIGURE 4 Patient C (see text): A hypercellular (80%) rim of parathyroid at the top of the image, surrounding a parathyroid adenoma. Hematoxylin-eosin stain, original magnification $\times 20$

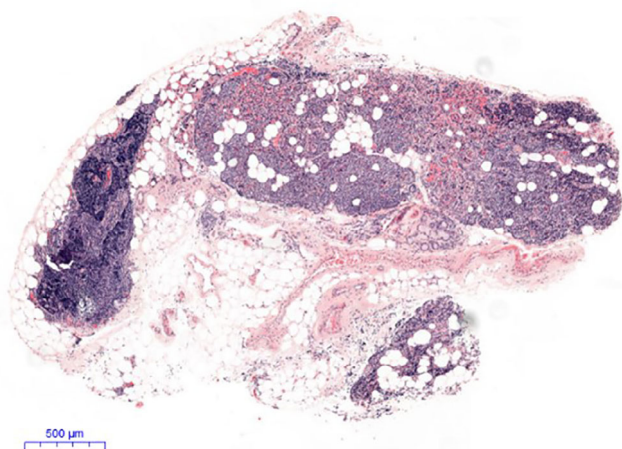


FIGURE 5 Patient C (see text): Parathyroid tissue from an incisional biopsy of a normal-appearing parathyroid showing parathyroid tissue with cellularity of $\sim 50\%$. Hematoxylin-eosin stain, original magnification $\times 20$

surgery to 4.1 mg/dL 2 weeks later, and remained elevated for more than 2 years of follow-up. Vitamin D was 60 nmol/L a month before surgery, remained similar in the following 2 weeks afterward, and was in the normal range for more than 2 years of follow-up. PTH level reduced from 213.8 pg/mL 3 months before surgery to 90.6 pg/mL 2 weeks later, and decreased to normal during a follow-up of more than 2 years. In a biopsy of other apparently normal glands, we estimated the cellularity level as 50% (see Figure 4). However, the cellularity level of the parathyroid tissue surrounding the adenoma was estimated as 80%, meaning it was hypercellular (see Figure 5).

There was no recurrence of PHPT for patients included in this study.

4 | DISCUSSION

This study assessed the correlation between high PTH after successful parathyroidectomy (long-term normal postsurgical calcium levels) and different demographic and clinical characteristics, especially cellularity level of the remaining parathyroid glands.

Contrary to our hypothesis, there was no correlation between the cellularity of the normal-appearing parathyroid glands and the parathyroid tissue surrounding the adenoma with PTH levels after surgery. This indicates that cellularity cannot be relied upon as a marker for elevated postoperative PTH levels in the presence of normal serum calcium and that an alternative explanation should be sought for this phenomenon. Some surgeons believe that if during surgery a parathyroid is observed and it is difficult to decide whether to resect it, it may be possible to send a biopsy for frozen sectioning, and if it is hypercellular, then they believe that a resection is appropriate. In the literature, we could find no support for this conduct, and we believe that our findings are discordant with it since, as was shown, many patients with a normal-sized parathyroid, but with hypercellular tissue left in situ did not have any medical consequences, as evidenced by normal PTH and calcium levels.

Also, the fact that we did not find a correlation between the cellularity level of the parathyroid tissue surrounding the adenoma and that of a normal-appearing parathyroid gland indicates that we cannot conclude the cellularity level in other parathyroid glands based on the pathological analysis of only the resected adenoma. We thought that possibly the difference in cellularity of the normal parathyroid can be explained by age however we did not find such a correlation ($R_s = -0.159$, $P\text{-value} = 0.28$), similar to previous studies.¹⁷

Similar to previous studies, we found a correlation of preoperative PTH levels with tumor dimensions¹⁸ and postoperative PTH levels were also correlated with tumor dimensions, as shown previously.¹⁹ In addition, we found a gender correlation with the weight of the adenoma, as men had heavier adenomas compared to women, as mentioned in other studies.²⁰

Schneider et al. suggested that a higher postoperative PTH was significantly associated with disease recurrence.²¹ This analysis comprised 1386 cases. Perhaps a comparatively small sample size in the present study explains the different findings.

Among the etiologies proposed for the phenomenon of normocalcemic-elevated hyperparathyroidism in the literature are physiological variation in the PTH due to relative postoperative hypocalcemia, vitamin D deficiency, a drop in the glomerular filtration rate (GFR), altered calcium-sensing receptors in the remaining glands leading to a higher set point for PTH secretion, reduced peripheral sensitivity to PTH, and renal calcium leakage.¹⁹ A statistically significant correlation between PTH postsurgery and other demographic or clinical characteristics, including vitamin D, calcium, and phosphorus levels, was not found in our study.

We believe that our findings are best explained by the hypothesis of the creation of resistance or decreased sensitivity to PTH due to the prolonged period of hyperparathyroidism, which results in changes at the PTH receptor or postreceptor level. As a result, after

parathyroidectomy, the patient maintains a higher PTH level than normal to maintain a normal calcium level. This explains the fact that the patients with larger tumors and a higher PTH tended to be those with a high PTH after surgery.

This study has several limitations. First, there is no prior research on the relationship between PTH levels postsurgery and the cellularity level of biopsies from healthy glands. Also, unfortunately, only one additional gland was biopsied in many of the cases, leaving the cellularity of the remaining glands that were not biopsied unknown. This limits interpretation of the results. In addition, some blood test results of the patients included in this study are lacking due to partial adherence to follow-up. IoPTH values are also unavailable, preventing an interesting comparison of %IoPTH drop between the groups. Additionally, a 24-hour urine test after surgery was not performed, may shed additional light on the high PTH phenomena, and should be addressed in future studies. Furthermore, due to the limited number of biopsies taken from healthy glands during parathyroidectomy in recent years, we were able to gather a sample size of only 47 patients, which is relatively small. Thus, future study of more patients is necessary.

5 | CONCLUSIONS

It appears that high PTH levels after successful parathyroidectomy in patients with primary hyperparathyroidism are not the result of hypercellular parathyroid glands that were not resected. Other factors should be further investigated.

ACKNOWLEDGMENTS

This study was conducted as part of the requirements for graduation from The Medical School of the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva Israel. We thank Professor Victor Novack and all the devoted workers of the Research Center in Soroka University Medical Center for their help in the realization of this study.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Ben-Zion Joshua: Study conception; inspection; design; results analysis and explanation; draft revisions. **Rotem Sagiv:** Data collection; manuscript draft preparation; writing the article. **Bertha Delgado:** Study design; pathological data analysis and explanation. **Re'em Sade:** Statistical consultation; analysis; draft revision. **Sagi Shashar:** Study design; statistical consultation; analysis. **Merav Frenkel:** Medical advising; study design; manuscript preparation. **Ksenya Yegodayev:** Technical guidance of glass slide scanning and analysis. **Moshe Elkabets:** Study design; technical guidance of glass slide scanning; draft preparation and revisions. All authors

reviewed the results and approved the final version of the manuscript.

ORCID

Rotem Sagiv  <https://orcid.org/0000-0003-0442-0339>

Ben-Zion Joshua  <https://orcid.org/0000-0002-2010-892X>

BIBLIOGRAPHY

1. Silverberg SJ, Lewiecki EM, Mosekilde L, Peacock M, Rubin MR. Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. *J Clin Endocrinol Metab.* 2009;94(2):351-365.
2. Mollerup CL, Vestergaard P, Frokjaer VG, Mosekilde L, Christiansen P, Blichert-Toft M. Risk of renal stone events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study. *BMJ.* 2002;325(7368):807.
3. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med.* 1999;341(17):1249-1255.
4. McDow AD, Sippel RS. Should symptoms be considered an indication for parathyroidectomy in primary hyperparathyroidism? *Clin Med Insights Endocrinol Diabetes.* 2018 11:112018.
5. Rubin MR, Bilezikian JP, McMahon DJ, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. *J Clin Endocrinol Metab.* 2008;93(9):3462-3470.
6. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014;99(10):3561-3569.
7. Silverberg SJ, Clarke BL, Peacock M, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014;99(10):3580-3594.
8. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg.* 2005;132(3):359-372.
9. Bartsch D, Nies C, Hasse C, Willuhn J, Rothmund M. Clinical and surgical aspects of double adenoma in patients with primary hyperparathyroidism. *Br J Surg.* 1995;82(7):926-929.
10. Maret A, Bourdeau I, Ding C, Kadkol SS, Westra WH, Levine MA. Expression of GCMB by intrathyroidic parathyroid hormone-secreting adenomas indicates their parathyroid cell origin. *J Clin Endocrinol Metab.* 2004;89(1):8-12.
11. Brown EM. Four-parameter model of the sigmoidal relationship between parathyroid hormone release and extracellular calcium concentration in normal and abnormal parathyroid tissue. *J Clin Endocrinol Metab.* 1983;56(3):572-581.
12. Ning L, Sippel R, Schaefer S, Chen H. What is the clinical significance of an elevated parathyroid hormone level after curative surgery for primary hyperparathyroidism? *Ann Surg.* 2009;249(3):469-472.
13. Oltmann SC, Maalouf NM, Holt S. Significance of elevated parathyroid hormone after parathyroidectomy for primary hyperparathyroidism. *Endocr Pract.* 2011;17(suppl 1):57-62.
14. Madkhali T, Alhefthi A, Chen H, Elfenbein D. Primary hyperparathyroidism. *Ulus Cerrahi Derg.* 2016;32:58-66.
15. Sathe PA, Madivale CV, Kandalkar BM, Bandgar TR, Shah NS, Menon PS. Primary hyperparathyroidism: A clinicopathological experience. *Indian J Pathol Microbiol.* 2009;52:313-320.
16. Rajan R, Poniecka A, Smith TL, et al. Change in tumor cellularity of breast carcinoma after neoadjuvant chemotherapy as a variable in the pathologic assessment of response. *Cancer.* 2004;100(7):1365-1373.

17. Dufour DR, Wilkerson SY. The normal parathyroid revisited: percentage of stromal fat. *Hum Pathol*. 1982;13(8):717-721.
18. Joshua B, Feinmesser R, Ulanovski D, et al. Primary hyperparathyroidism in young adults. *Otolaryngol Head Neck Surg*. 2004;131(5):628-632.
19. de la Plaza LR, Ramia Angel JM, Arteaga Peralta V, et al. Elevated parathyroid hormone levels after successful parathyroidectomy for primary hyperparathyroidism: a clinical review. *Eur Arch Otorhinolaryngol*. 2018;275(3):659-669.
20. Mazeh H, Sippel RS, Chen H. The role of gender in primary hyperparathyroidism: same disease, different presentation. *Ann Surg Oncol*. 2012;19(9):2958-2962.
21. Schneider DF, Mazeh H, Chen H, Sippel RS. Predictors of recurrence in primary hyperparathyroidism: an analysis of 1386 cases. *Ann Surg*. 2014;259:563-568.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Sagiv R, Delgado B, Sadeh R, et al. High parathyroid hormone levels after parathyroidectomy for parathyroid adenoma are not related to the cellularity of the remaining glands. *Laryngoscope Investigative Otolaryngology*. 2021;6(5):1220-1227. doi:10.1002/lio2.644