Asian Journal of Surgery 45 (2022) 407–411

Contents lists available at ScienceDirect

Asian Journal of Surgery

journal homepage: www.e-asianjournalsurgery.com

Original Article

Association of biochemical and clinical parameters with parathyroid adenoma weight. Turkish-Bulgarian endocrine and breast surgery study group, hyperparathyroidism registry study

Beyza Özçınar [a, *], Gizem Öner [b, c, d], Özer Makay [e], Aykut Soyder [f], N. Zafer Cantürk [d], M. Ümit Uğurlu [g], Y. Atakan Sezer [h], Semih Görgülü [i], Mustafa Girgin [j], A. İbrahim Özemir [k], Serdar Özbaş [f], Bülent Ünal [l], Rumen Pandev [m], Serap Erel [n], A. Uğur Emre [o], A. İlker Filiz [p], M. Nuran Akçay [q], Salih Demircioğlu [g], S. Ata Güler [d], Erkan Öztürk [i], Ramazan Yıldız [i], Güldeniz Karadeniz Çakmak [o], Yavuz Kurt [p], Yeşim Erbil [a], Bahadır M. Güllüoğlu [g]

[a] Department of General Surgery, Istanbul University, Istanbul School of Medicine, Istanbul, Turkey
[b] Multidisciplinary Oncologic Centre Antwerp (MOCA), Antwerp University Hospital, Edegem, Belgium
[c] Center for Oncological Research (CORE), University of Antwerp, Wilrijk, Belgium
[d] Department of General Surgery, Kocaeli University School of Medicine, Kocaeli, Turkey
[e] Department of General Surgery, Division of Endocrine Surgery, Ege University School of Medicine, İzmir, Turkey
[f] Department of General Surgery, Adnan Menderes University School of Medicine, Aydin, Turkey
[g] Department of General Surgery, Marmara University School of Medicine, Istanbul, Turkey
[h] Department of General Surgery, Trakya University School of Medicine, Edirne, Turkey
[i] Department of General Surgery, Gülhane Training and Research Hospital, Ankara, Turkey
[j] Department of General Surgery, Fırat University School of Medicine, Elazığ, Turkey
[k] Department of General Surgery, Istanbul Medeniyet University School of Medicine, Istanbul, Turkey
[l] Department of General Surgery, Inönü University School of Medicine, Malatya, Turkey
[m] Department of General Surgery, Division of Endocrine Surgery, Tsaritsa Yoanna University School of Medicine, Sofia, Bulgaria
[n] Department of General Surgery, Ankara Training and Research Hospital, Ankara, Turkey
[o] Department of General Surgery, Bülent Ecevit University School of Medicine, Zonguldak, Turkey
[p] Department of General Surgery, Gülhane Training and Research Hospital, Istanbul, Turkey
[q] Department of General Surgery, Atatürk University School of Medicine, Erzurum, Turkey

ARTICLE INFO

Article history:
Received 3 May 2021
Received in revised form
10 June 2021
Accepted 28 June 2021
Available online 2 August 2021

Keywords:
Hyperparathyroidism
Regional differences
Adenoma weight
Biochemical markers

SUMMARY

Background: Primary hyperparathyroidism (pHPT) caused by a single benign parathyroid adenoma is a common endocrine disorder that is affected by regional differences. Living in different geographical regions reveals differences in the laboratory results and pathological findings, but studies on this subject are not sufficient. The article focuses on biochemical and pathological effects of geographical differences in parathyroid adenoma. In addition, the present study seeks to elaborate on treatment methods and effectiveness of screening in geographical area of Bulgaria and Turkey.

Method: In this prospective study, 159 patients were included from 16 centres. Demographic characteristics, symptoms, biochemical markers and pathologic characteristics were analysed and compared between 8 different regions.

Results: Patients from Turkish Black Sea had the highest median serum calcium (Ca) level, whereas patients from Eastern Turkey had the lowest median serum phosphorus (P) level. On the other hand, there was no significant difference between Ca, parathormone (PTH) and P levels according to regions. Patients from Eastern Turkey had the highest adenoma weight, while patients from Bulgaria had the lowest adenoma weight. The weight of adenoma showed statistically significant differences between regions ($p < 0.001$). There was a correlation between adenoma weight and serum PTH level ($p = 0.05$) and Ca level ($p = 0.035$).

* Corresponding author. Department of General Surgery, Istanbul University, Istanbul School of Medicine, Istanbul, Turkey.
E-mail address: drbeyza@hotmail.com (B. Özçınar).

https://doi.org/10.1016/j.asjsur.2021.06.035

Conclusion: This study has provided a deeper insight into the effect of the regional differences upon clinicopathological changing and biochemical values of pHTP patients with adenoma. Awareness of regional differences will assist in biochemical screening and treatment of this patient group.

1. Introduction

Primary hyperparathyroidism (pHPT) is a third common endocrine disorder, which is characterized by an excessive parathyroid hormone (PTH) secretion from one or more of the four parathyroid glands. A single benign parathyroid adenoma is the most common cause of pHPT. Classical pHPT mostly presented with different symptoms such as kidney stones and bone fracture in the 1970s.[1] Recently, pHPT has become more routinely diagnosed at an asymptomatic stage due to increased screening of the serum calcium level that is the main regulator of the PTH secretion.[2] The clinical change of PHP from symptomatic to asymptomatic also changes the treatment and surgical decision to be applied to the patient.

A global level epidemiological concept implementation for primary hyperparathyroidism is problematic because there is not any uniform test to measure the serum calcium level in different regions. In addition, the symptoms of disease and the treatment ways in practice are also changing. It appears that in Europe and United State, pHPT is diagnosed commonly as an asymptomatic disorder.[2–5] On the other hand, patients with pHPT in Asian countries such as India, Iran and Thailand still mostly present with an organ manifestation.[6–10] Research has demonstrated that geographic disparity may affect the clinical and pathological features of pHPT.[11,12] Although considerable research has been devoted to pHPT disorder treatment, less attention has been paid to geographical factors effect in pHPT with adenoma.

The aim of this study is to reveal the biochemical and pathological effects of geographical differences in parathyroid adenoma. This article also elucidates the changes in the diagnosis and treatment of parathyroid adenoma in geographical area of Bulgaria and Turkey.

2. Materials and methods

This study is a prospective study, which was conducted by the 15 centres in Turkey and one centre in Bulgaria. It is critical to appreciate the true impact of the different geographical regions in patients pHPT treated with parathyroidectomy. For this reason, the data were classified according to 8 different regions as in our retrospective study: [1]Bulgaria, [2]Marmara, [3]Turkish Aegean, [4]Turkish Mediterranean, [5]Central Turkey, [6]Turkish Black Sea, [7]Eastern Turkey and [8]South-East Turkey (Fig. 1-a,b). Between January and July 2014, 159 patients were included in this study from 16 centres. Patients with parathyroid carcinoma, MEN-or familial- related disease and chronic kidney disease were excluded. Demographic characteristics, symptoms, serum total calcium (Ca), phosphorus (P), Alkaline Phosphatase (ALP), serum parathormone (PTH) levels and serum 25-hydroxy (OH)- vitamin D levels were analysed and compared between the 8 different regions. In addition to these, diagnostic modalities such as ultrasound (USG), schintigraphy, computerized tomography (CT), magnetic resonance imaging (MRI) were evaluated. Furthermore, the data was also analysed according to pathologic characteristics and type of operation. The findings were discussed in relation to the different regions.

Asymptomatic pHPT patients were determined for surgery according to the 2014 guidelines for the management of asymptomatic pHPT of the fourth international workshop. Patients' total calcium concentrations were adjusted to the serum albumin concentration. Vitamin D deficiency threshold was defined as a serum 25-OH- vitamin D level below 50 nmol/L (20 ng/mL). For normocalcemic pHPT patients secondary causes of hyperparathyroidism were ruled out. Secondary and tertiary hyperparathyroidism patients were excluded from the study. Non-decreased Ca and PTH levels after surgery, or raising again in first 6 months after surgery were also considered as persistent disease and the treatment was considered unsuccessful.

2.1. Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Science release 22.0 for Windows software package (SPSS; IBM Inc., Chicago, USA). The demographic characteristics of patient according to regions were evaluated using descriptive statistic means, medians and standard deviation. Differences between the various clinical, pathological and treatment variables across the 8 separate regions were analysed using the paired sample T test and Wilcoxon for the comparison of continuous depended variables between groups and the Mann-Whitney U test was used for the independent non-parametric variables. The chi-squared test or Fisher exact test where appropriate for the comparison of categorized variables. One-Way ANOVA and Kruskal Wallis tests were used to compare more than 2 groups. Homogeneity and normality of numeric variables were analysed using the Kolmogorov-Smirnov test. A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Demographic and laboratory characteristics

We identified a total of 159 patients who underwent parathyroidectomy between January 2014 and July 2014. Median age was 52 (19–84) years and 81 % (n = 129) were female. The demographic and laboratory characteristics of the patients by regions are shown in Table 1. Most of the patients (76 %) were admitted to clinic with symptoms and median time of the symptoms is 9.5 (1–96) months, while the number of asymptomatic patients was 38 (24 %). The median preoperative Ca level was 11.3 (8.3–15.1) mg/dL and serum PTH level was 207.5 (50–5000) pg/mL. Moreover, preoperative P level was 2.5 (1.3–4.8) mg/dL and ALP 104.5 (9–6490) U/L. On the other hand, vitamin D deficiency was detected in 127 patients (80 %). Patients from Turkish Black Sea had the highest median serum Ca level (12.05 mg/dL), whereas patients from Eastern Turkey had the lowest median serum P level (2.3 mg/dl). However, there was no significant difference between age, gender, Ca, PTH, P and ALP levels according to regions (Table 1).

3.2. Surgical procedure and pathological diagnosis

Minimally invasive parathyroid (MIP) surgery was used as a

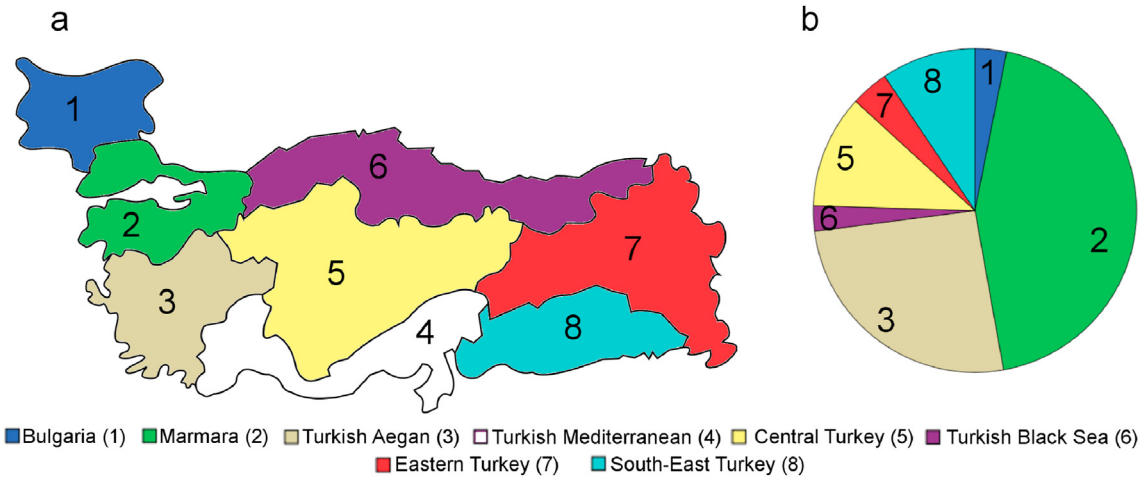

Fig. 1. a and b. Geographical regions included in this study.

Table 1
Demographic and laboratory characteristics of patients by regions.

Region	1	2	3	4	5	6	7	8	P
n (%)	5 (3.2)	70 (44)	41 (25.8)	–	18 (11.3)	4 (2.5)	6 (3.8)	15 (9.4)	NS
Gender (Female/Male)	5/0	55/15	38/3	–	11/7	4/0	5/1	11/4	NS
Symptomatic patient rate (n)	4	53	33	–	14	2	2	13	NS
Asymptomatic patient rate	1	17	8	–	4	2	4	2	NS
Preoperative Ca values (mg/dL) median (min–max)	11.7 (11.5–13.3)	11.2 (8.3–14.4)	11.4 (10.0–14.6)	–	11.65 (10.5–15.1)	12.05 (10.4–13.7)	10.7 (10.5–12.0)	11.3 (9.4–12.8)	NS
Preoperative P values (mg/dL) median (min–max)	3.1 (2.3–4.3)	2.7 (1.6–4.6)	2.5 (1.3–3.8)	–	2.4 (1.5–3.4)	2.9 (2.0–3.1)	2.3 (2.1–3.1)	2.6 (1.3–4.8)	NS
Preoperative PTH values (pg/mL) median (min–max)	208 (107–428)	198 (50–5000)	199 (68–2286)	–	226 (121–970)	500.5 (138–1177)	219 (135–272)	216 (79–1648)	NS
Preoperative ALP values (U/L) median (min–max)	133 (85–233)	101 (31–650)	98.5 (38–1005)	–	105.5 (68–278)	140 (62–376)	103 (70–133)	114 (72–429)	NS
25-OH vitamin D deficiency (%)	100	75	82.1	–	61.1	100	83.3		NS

PTH: parathormone, NS: not significant.

Table 2
Surgical procedure and pathological diagnosis of patients by regions.

Region	1	2	3	4	5	6	7	8	P
Surgical Procedure (n)									NS
• Conventional	2	32	8	–	5	2	4	15	
• Minimally invasive	3	38	22	–	12	2	2	–	
• Totally endoscopic	–	–	–	–	–	–	–	–	
• Video-assisted	–	–	9	–	–	–	–	–	
• Radio-guided	–	–	2	–	1	–	–	–	
Pathological diagnosis (n)									NS
• Hyperplasia	1	7	–	–	–	–	–	3	
• Adenoma	4	60	40	–	17	4	6	12	
• Atypical adenoma	–	2	–	–	1	–	–	–	
• Carcinoma	–	1	1	–	–	–	–	–	
Adenoma number									NS
• 1	3	60	39	–	18	4	5	11	
• 2	1	3	2	–	–	–	1	1	
• >2	–	–	–	–	–	–	–	–	
Adenoma weight (mg) median (min–max)	19 (9–58)	846.7 (39–6000)	1000 (100–6490)	–	1700 (600–4600)	220 (170–310)	2150 (1843–5000)	980 (200–1560)	<**0.001**

NS: not significant.

surgical method in 49.7 % (n = 79) of patients, while conventional approach was used in 42.8 % (n = 68) of patients. All patients in the South-East Turkey (n = 15) were operated with the conventional approach. Parathyroid adenoma was diagnosed in 143 patients and only eight of them had two adenomas. More than two adenomas were not detected in any patient (Table 2).

The median adenoma weight was 1000 mg (9–6490). Patients from Eastern Turkey had the highest adenoma weight (1843–5000), while patients from Bulgaria had the lowest adenoma weight (9–58). The weight of adenoma showed statistically significant differences between regions ($p < 0.001$) (Table 2). No correlation was showed between adenoma weight and age, sex or duration of symptoms. There was a statistically positive correlation between adenoma weight and serum PTH level ($p = 0.05$), Ca level ($p = 0.035$) and ALP level ($p < 0.001$). On the other hand, a negative correlation between adenoma weight and 25- OH- vitamin D level ($p = 0.04$) and P level ($p = 0.05$) were seen.

Complications occurred in three patients (1, 9 %). Wound infection was detected in one patient and temporary unilateral vocal cord paralysis in one patient. One patient was reoperated for persistent hyperparathyroidism.

4. Discussion

Parathyroid adenoma is the most common cause of pHPT and this study finds strong evidence that for a parathyroid adenoma weight has a correlation with biochemical parameters. First time, Rutledge et al indicated a relationship between preoperative serum PTH and calcium level with gland weight or volume.[13] Bindlish et al demonstrated that there was a significant correlation between PTH and adenoma weight and also showed that there is a negative weak correlation between adenoma weight and phosphate level.[14] Kamani et al also reached conclusions that there were a correlation between adenoma weight and serum PTH and calcium levels. On the other hand, preoperative serum P had no predictive value on adenoma weight.[15] Some research has demonstrated no relationship between serum markers of pHPT and adenoma weight and/or size.[16–18] Rao DS et al contended that there was a significant inverse relation between adenoma weight and serum levels of 25-OH-vitamin D. A detailed explanation is that 25-OH- vitamin D deficiency decreases Ca sensitivity of PTH and therefore a higher PTH level is required to have the same effect. As a result, parathyroid cells also develop hypertrophy.[19] Our results are similar in many aspects to those from previous studies on positive correlation between adenoma weight and serum PTH and calcium levels. This study showed there is a negative correlation between 25- OH-vitamin D level and P level with respect to parathyroid adenoma weight. This study also demonstrated that adenoma weight had statistical significant differences between the regions. It is the highest in Eastern Turkey, but it is the lowest in Bulgaria region. Well, the calcium level is the lowest in Eastern Turkey, and the adenoma weight is the highest so how we can explain this conflict? The Eastern region and South-East region are less developed regions in Turkey and also per capita income is the lowest. As a result, the rate of people going to the doctor for a routine follow up is lower. Therefore, since most of the patients consult a doctor after being symptomatic, the adenoma weight may be higher because of the late diagnosis. These results also show us that, it would be beneficial to take Ca and PTH tests for routine screening programme especially in Eastern regions.

There have been changes in the surgical methods over the years with successful preoperative localization of a parathyroid adenoma. Parathyroidectomy (PTx) is the curative approach to pHPT with adenoma. It is indicated in those with symptomatic pHPT and asymptomatic pHPT who meets the surgical guideline criteria.[20] Minimally invasive parathyroid (MIP) surgery has become widely used. MIP has 95–98 % surgical success rates and 1–3% complication rates similar to those seen with the conventional open PTx. If preoperative imaging has not identified a parathyroid adenoma or if hyperplasia or familial disease is suspected, a conventional PTx is preferred.[20–22] This study confirms the increase in the choice of MIP when it is compared to our retrospective study data. While 34 % of patients underwent MIP in our previous study,[12] this rate increased to 49.7 %. However, conventional surgery is still preferred in the South-East Turkey region. The South-East Region is the least developed region of Turkey and where technology and advances in medicine have been applied later.

Comparing prevalence and clinical aspects of pHPT within a country and between countries is problematical because of varying levels of screening availability and sources of information. Unfortunately, this study did not directly shed light on the incidence of pHPT and parathyroid adenoma in our geographical region. Because, there is no formal data showing the exact numbers of pHPT and parathyroid adenoma cases in different regions of Turkey and also Bulgaria. However, this study pointed that the majority of patients were still diagnosed during the symptomatic period. In the 1930s at the Massachusetts General Hospital, patients diagnosed with pHPT had kidney stones in 57 %, peptic ulcer disease in 8 %, and bone complications in 23 %.[23] Recently, we no longer encounter such a clinical case presentation. Due to the increased screening methods, it began to be diagnosed more routinely with a milder symptom or an asymptomatic stage. The clinical change of pHPT from symptomatic to asymptomatic occurred primarily in the USA and Europe.[2] Our results demonstrated that 24 % of the patients were diagnosed in the asymptomatic period. This was shown as a relevant indicator that more attention should be paid to the biochemical screening of pHPT.

There are studies showing that geographical differences also caused to clinical and biochemical differences in patients with pHPT.[11,12,24] Relative to our retrospective study, the highest preoperative serum Ca level was observed in the Black Sea region (both in Bulgaria and Turkish Black Sea region).[12] Additionally, the lowest serum P level was found in Eastern Turkey. In this study, the highest median value of Ca was showed in the Black Sea region and the lowest median value of P was observed in Eastern Turkey. Although the results were in line with the previous research results in this study, there was statistically significant differences between the regions this time. What are the features of these regions to explain these differences: Turkey is a country consisting of a total of seven regions, and geographically located in both Asia and Europe, with a surface area of 783,562 km2. The Marmara region is located on Europe and the other regions in Asia. There are different environmental factors and life habits between Western side of Turkey and Eastern side. Therefore, Turkey is surrounded by seas on 3 sides, and each geographical region has different climatic conditions. The Black Sea region and Bulgaria (is a neighbor of Turkey from Black Sea side and located at South-East Europe) are similarly located on the Black Sea coast and The Black Sea region receives excessive rain throughout the year and the Ca ratio of sea water increases depending on the rain water (desalinated water has 20 times more Ca than salty water), unlike other regions. In addition, people consume large amounts of seafood in Black Sea region. On the other hand, the Eastern and South-East regions are not located by the sea and the seafood consumption rate of the people in these regions is very low and there may also be genetic differences in Ca metabolism in different regions.

In spite of the effective results of this research, there were some limitations. First of all, the number of patients was not equal to eight regions and there was not any patient from Turkish Mediterranean region. The population density in Turkey is the highest in

Marmara with 24 million 465 thousand 194, and the least in Eastern Turkey with 5 million 966 thousand 101. In addition, the population density in other regions was determined in the Mediterranean Region with 10 million 552 thousand 942 people, in the Aegean Region with a population of 10 million 318 thousand 157, in the South-East Region with a population of 8 million 876 thousand 531, and in the Black Sea Region with a population of 7 million 674 thousand 496. A population of 1.67 million lives in the Sofia region. There is a correlation between population density and the number of patients, but this study was carried out by 16 centers. In other words, not every hospital in this geographic area was involved in this study. Therefore, a general conclusion about the total number of patients in the regions cannot be reached with the current study. Lastly, low number of patients included in the study. This is related to the inclusion of patients who were diagnosed and treated between January and July and also the number of centers involved in the study.

5. Conclusion

Regional differences have an impact on the pathological and biochemical values of parathyroid adenoma and parathyroid adenoma weight has a correlation with biochemical parameters. Moreover, the diagnosis of patients in the symptomatic period indicates that more attention should be paid to the biochemical screening of pHPT. Further research is imperative to improve our understanding of the geographic factors and its association with pHPT.

Funding

No funding

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethics approval and consent to participate

Authors declare that the subjects have given their informed consent and that the study protocol has been approved by the institute's committee on human research.

Authors' contributions

All authors have contributed to the conception and design of the work and the analysis of the data in a manner substantial enough to take public responsibility for it; each believes the manuscript represents valid work; and each has reviewed the final version of the manuscript and approves it for publication. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Availability of data and material (data transparency):

Acknowledgements

Not applicable.

References

1. Pallan S, Rahman MO, Khan AA. Diagnosis and management of primary hyperparathyroidism. *BMJ*. 2012;344:1013.
2. Bilezikian JP, Silverberg SJ. Clinical practice. Asymptomatic primary hyperparathyroidism. *N Engl J Med*. 2004;350:1746–1751.
3. Palmer M, Jakobsson S, Akerstrom G, Ljunghall S. Prevalence of hypercalcaemia in a health survey: a 14-year follow-up study of serum calcium values. *Eur J Clin Invest*. 1988;18:39–46.
4. Abood A, Vestergaard P. Increasing incidence of primary hyperparathyroidism in Denmark. *Dan Med J*. 2013;60:4567.
5. Rao SD. Epidemiology of parathyroid disorders. *Best Pract Res Clin Endocrinol Metabol*. 2018;32:773–780.
6. Pradeep PV, Jayashree B, Mishra A, Mishra SK. Systematic review of primary hyperparathyroidism in India: the past, present, and the future trends. *Internet J Endocrinol*. 2011;2011:921814.
7. Prasarttong-Osoth P, Wathanaoran P, Imruetaicharoenchoke W, Rojananin S. Primary hyperparathyroidism: 11-year experience in a single institute in Thailand. *Internet J Endocrinol*. 2012, 952426.
8. Shah VN, Bhadada S, Bhansali A, Behera A, Mittal BR. Changes in clinical and biochemical presentations of primary hyperparathyroidism in India over a period of 20 years. *Indian J Med Res*. 2014;139:694–699.
9. Hamidi S, Soltani A, Hedayat A, Kamalian N. Primary hyperparathyroidism: a review of 177 cases. *Med Sci Monit*. 2006;12:CR86–C89.
10. Bilezikian JP, Cusano NE, Khan AA, Liu JM, Marcocci C, Bandeira F. Primary hyperparathyroidism. *Nat Rev Dis Primers*. 2017;2, 16033. https://doi.org/10.1038/nrdp.2016.33.
11. Kirdak T, Duh QY, Kebebew E, Clark OH. Do patients undergoing parathyroidectomy for primary hyperparathyroidism in San Francisco, CA, and Bursa, Turkey, differ? *Am J Surg*. 2009;198:188–192.
12. Makay O, Ozcinar B, Simsek T, et al. Regional clinical and biochemical differences among patients with primary hyperparathyroidism. *Balkan Med J*. 2017;34:28–34.
13. Rutledge R, Stiegel M, Thomas Jr CG, Wild RE. The relation of serum calcium and immunoparathormone levels to parathyroid size and weight in primary hyperparathyroidism. *Surgery*. 1885;98:1107–1112.
14. Bindlish V, Freeman JL, Witterick IJ, Asa SL. Correlation of the biochemical parameters with single parathyroid adenoma weight and volume. *Head Neck*. 2002;24:1000–1003.
15. Kamani F, Najafi A, Mohammadi SS, Tvassoli S, Shojaei SP. Correlation of biochemical markers of primary hyperparathyroidism with single adenoma weight and volume. *Indian J Surg*. 2013;75(2):102–105.
16. Wagner PK, Rothmund M. Correlation of tumor weight and typical pathologic laboratory parameters in primary hyperparathyroidism. *Langenbecks Arch Chir*. 1983;360:133–139.
17. Randhawa PS, Mace AD, Nouraei SA, Stearns MP. Primary hyperparathyroidism: do perioperative biochemical variables correlate with parathyroid adenoma weight or volume? *Clin Otolaryngol*. 2007;32:179–184.
18. Saxe AW, Lincenberg S, Hamburger SW. Can the volume of abnormal parathyroid tissue be predicted by preoperative biochemical measurem. *Surgery*. 1987 Nov;102(5), 840e845.
19. Rao DS, Honasoge M, Divine GW, et al, et al.. Effect of vitamin D nutrition on parathyroid adenoma weight: pathogenetic and clinical implications. *J Clin Endocrinol Metab*. 2000;85:1054–1058.
20. Udelsman R, Akerstrom G, Biagini C, et al. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99:3595–3606.
21. Udelsman R, Lin Z, Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. *Ann Surg*. 2011;253:585–591.
22. Van Udelsman B, Udelsman R. Surgery in primary hyperparathyroidism: extensive personal experience. *J Clin Densitom*. 2013;16:54–59.
23. Cope O. The study of hyperparathyroidism at the Massachusetts General Hospital. *N Engl J Med*. 1966;274:1174–1182.
24. De Lucia F, Minisola S, Romagnoli E, et al. Effect of gender and geographic location on the expression of primary hyperparathyroidism. *J Endocrinol Invest*. 2013;36:123–126.