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Characteristics of patients operated for primary hyperparathyroidism at university hospitals in Türkiye: differences among Türkiye's geographical regions

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Purpose: The aim of this study was to define the clinical and laboratory characteristics of patients operated on for primary hyperpatathyroidism (PHPT) at university hospitals in Türkiye, and to investigate the differences in the clinical presentations of the disease between different geographical regions.
Methods: Patients operated on for PHPT in the university hospitals of Türkiye were included in the study. The demographic, clinical, and laboratory findings and the operational data of the patients were investigated according to the whole country and to different geographical regions. Comparisons were performed according to whole country and regions.
Results: A total of 1,162 cases were included in the study from different regions and 20 university hospitals. The mean age of patients was 52.4 ± 0.38 (mean ± standard error) in the general population of Türkiye. The rates of hypertension, urolithiasis, bone disease and 25-hydroxyvitamin D insufficiency were 35%, 18.6%, 67.6%, and 63%, respectively. The median parathormone (PTH), serum total calcium (Ca^{+2}) and phosphorus value were 220 pg/mL (range, 70–2,500 pg/mL), 11.2 mg/dL (range, 9.5–11.2 mg/dL), and 2.4 mg/dL (range, 1–4.7 mg/dL), respectively. The median size of the adenomas resected was 16 mm (range, 4–70 mm). Significant differences were observed in the clinical and laboratory findings of the patients operated on due to PHPT between different geographical regions of Türkiye ($P < 0.05$).
Conclusion: The clinical and laboratory characteristics of the patients with PHPT in different geographical regions of Türkiye differ. Furthermore, the general findings of the cases in Türkiye give us a hint that the severity of the disease here is somewhere between Eastern and Western countries.
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Key Words: Primary hyperparathyroidism, Parathyroidectomy, Turkey

INTRODUCTION

Most of the studies on primary hyperpatathyroidism (PHPT) and parathyroidectomy are generally of West Europe or North America origin. Therefore, when the clinical and laboratory presentations of the disease are defined, the data are generally from North American and Western Europe [1,2]. However, it has been demonstrated in comparative studies that PHPT may have different clinical presentations in different geographical regions [1,3-5]. For example, in a study comparing the female cases with PHPT between New York, United States, and Beijing, China, clinical findings such as osteoporosis, urolithiasis and osteitis cystica fibrosa were found to be more frequent, the parathormone (PTH) and Ca^{+2} levels were found to be higher, and 25-hydroxyvitamin D (25(OH)D) level was found to be lower in women living in Beijing. However, in the same study, asymptomatic PHPT was found to be more common in women living in New York [1]. Likewise, in another study comparing

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patients in San Francisco, United States and Bursa, Türkiye matched according to age and gender, osteoporosis was more frequent, the PTH level was higher, the phosphorus level was lower, and the adenoma sizes were larger in patients living in Bursa [3]. However, such studies conducted in a certain region of countries may not give enough information for the whole country. Of this socio-economic, ethnic or climate-related differences may be observed in patients of different geographical regions of a country with a large surface area. This may lead to the presentation diseases with different clinical and laboratory findings within the same country.

Considering this subject, the present information in the literature is insufficient with regard to the clinical, laboratory, and operational data of the patients operated on due to PHPT that reflect the general population of Türkiye. Furthermore, no difference was considered for the clinical presentation of the disease in different geographical regions of Türkiye, which is a quite large country with regard to the surface area and population. The aim of this study was to define the clinical and laboratory characteristics of patients operated on for PHPT at university hospitals in Türkiye, and to investigate the differences in the clinical presentations of the disorder between different geographical regions.

METHODS

The study included patients operated on for PHPT at university hospitals in Türkiye between January 2004 and December 2008. The data were obtained from patient files and electronic records retrospectively. The number of general surgical operations between the dates of the study in participating hospitals was also recorded. The participating hospitals had recorded the data in a standard electronic form, in the Excel program. The demographic, clinical, laboratory and operational findings of the whole country and regions of Türkiye were investigated. Additionally, comparisons were performed with regard to the general country and different regions. The study was approved by the Ethical Committee of Scientific Researchs of the hospital in charge.

Determining the centres to provide data to the study

The number of patients operated on due to PHPT in Türkiye is limited. The diagnosis and treatment of the disease is generally performed by certain reference medical centres. Therefore, university hospitals in different regions of the country, which are believed to be reference centres, were included in the study in order to obtain larger patient series. A total of 25 university hospitals to be included in the study; however, only 21 universities agreed to participate. One of the 21 hospitals had insuffient data and was therefore excluded. The study was completed with a total of 20 university hospitals.

Determining the regions

The classically predefined 7 regions were considered when investigating the distribution of the disease throughout Türkiye. However, the East Anatolian region and the Southeast Anatolian region were combined, since the data of patients with PHPT obtained in each region were considered to be insuffiecient, and named East-Southeast Anatolian region. Accordingly, the country was then divided into 6 regions. Besides this, centres in the Karadeniz region could not provide sufficient data, and therefore, this region was not included, and Türkiye was investigated as 5 regions (Table 1).

Presentation of data on tables

Since this study was retrospective, the total number of cases investigated for each parameter was different. Therefore, for certain parameters investigated, the total number of patients who possessed data for those parameters was expressed in the tables.

Table 1. Distribution of cases according to regions and university hospitals in Türkiye

Region/city	No. of cases (%)
Marmara region	434 (37.3)
İstanbul University, Cerrahpasa Medical Faculty/İstanbul	75
İstanbul University Medical Faculty/İstanbul	157
Marmara University/Istanbul	27
Kocaeli University/Kocaeli	75
Uludag University/Bursa	100
Aegean region	150 (12.9)
Ege University/Izmir	75
Adnan Menderes University/Aydin	35
Pamukkale University/Denizli	40
Mediterranean region	67 (5.8)
Cukurova University/Adana	44
Mersin University/Mersin	23
Central anatolia region	396 (34.1)
Erciyes University/ Kayseri	70
Hacettepe University/Ankara	112
Ankara University/Ankara	95
Gazi University/Ankara	75
Osmangazi University/Eskisehir	19
Cumhuriyet University/Sivas	25
East-Southeast anatolian region	115 (9.9)
Atatü University/Erzurum	53
Dicle University/Diyarbakir	8
Gaziantep University/Gaziantep	16
Firat University/Elazig	38
Total	1,162

Statistical analysis

The comparisons were performed between the general data of Türkiye and the data of the regions. Interregional comparisons were performed as well. The continuous variables were expressed as mean ± standard error or median (range), while the categorical variables were presented as frequency with related percentage. The comparisons between the groups were performed using the Kruskal-Wallis or the analysis of variance (ANOVA) test, to determine whether the variables followed a normal distribution or not. The Bonferroni test was performed for multiple comparisons after the ANOVA test. Two-group comparisons were performed using the Mann-Whitney test. The comparisons of the categorical variables between the groups were performed using the Fisher-Freeman-Halton test, the Pearson chi-square test or the Fisher Exact test. Statistical analyses were also performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA), and the level of siginificance was set at α=0.05.

RESULTS

The general surgery clinics of 20 university hospitals from 5 different regions were included in the study. The total number of cases investigated was 1,228. However, 66 cases were excluded due to various reasons such as high creatinine levels or the operation date being out of the interval accepted in the study. Therefore, the total number of cases included was 1,162. When the distribution of the cases according to the regions was investigated, regions with the highest number were the Marmara (n=434, 37.3%) and the Central Anatolian regions (n=396, 34%). The region with the lowest number was the Mediterranean (n=67, 5.8%) (Table 1). However, it should be considered that the cases of East and Southeast Anatolia were combined and the data were included as the East-Southeast Anatolian Region.

Thirteen out of 20 centres participating in the study had sent the data of general surgical operations performed within the dates of the study. According to these data, 169,527 general surgical operations and 732 parathyroidectomies were performed. These data indicate that the rate of parathyroidectomies performed due to PHPT in the university hospitals of Türkiye among all general surgical operations was 0.4%. The distribution in years indicated that the number of cases operated due to PHPT in Türkiye increased (Fig. 1).

Demographic and clinical findings

Nine hundred fifty-seven of the cases (82.4%) operated on due to PHPT in the university hospitals of Türkiye were women and 205 (17.6%) were men. No difference was determined between the regions with regard to gender (P > 0.05).

The mean age was 52.4 ± 0.38 years. The mean ages of the women and men were 52.07 ± 0.42 and 54.03 ± 0.38 years, respectively, which indicated no statistical significance (P = 0.542). Cases in the East-Southeast Anatolian Region were observed to be younger than the cases in both Türkiye's general area and Marmara, Aegean and Central Anatolian Regions (P < 0.001). The Mediterranean Region included the youngest patients following East-Southeast Anatolian Region, and had similar age with the remaining regions (Table 2).

The rate of cases operated on due to recurrence or persistent PHPT in the university hospitals of Türkiye was 3.9%. No difference was detected between the regions (P = 0.377) or

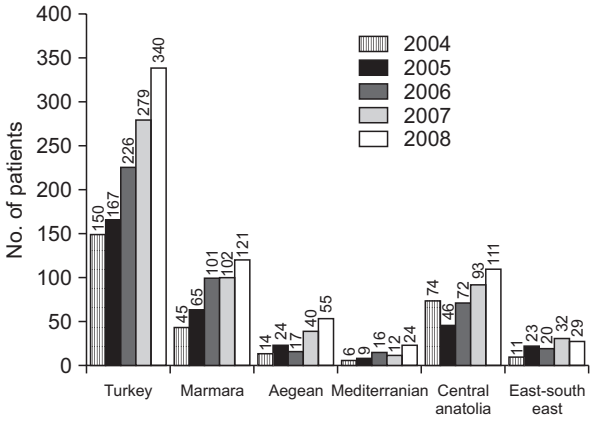

Fig. 1. Distribution of patients with primary hyperpatathyroidism according to years and regions in Türkiye.

Table 2. Demographic and clinical data of patients undergoing surgery for PHPT at university hospitals in Türkiye

Variable	Türkiye	1	2	3	4	5	P-value[a]	P-value[b]
Female/male	957/205	369/65	117/33	51/16	322/74	98/17	0.146	0.054
Age (yr)	52.4 ± 0.38	52.4 ± 0.63	53.9 ± 1.01	50.1 ± 1.50	53.7 ± 0.64	46.8 ± 1.34	<0.001	<0.001
Previous PTx	43/1,116 (3.9)	21/428 (4.9)	4/110 (3.6)	2/67 (3)	15/396 (3.8)	1/115 (0.9)	0.377	0.522
Hypertension	388/1,100 (35.3)	138/399 (34.6)	52/147 (35.4)	26/57 (45.6)	139/391 (35.5)	33/106 (31.1)	0.469	0.614
Urolithiasis	206/1,109 (18.6)	84/420 (20)	29/146 (19.9)	21/47 (44.7)	54/385 (14)	18/111 (16.2)	<0.001	<0.001

Values are presented as mean±standard error or number/N (%).
PHPT, primary hyperparathyroidism; PTx, parathyroidectomy; N, total cases who have data related that parameter.
Regions: 1, Marmara; 2, Aegean; 3, Mediterranean; 4, Central Anatolia; 5, East-Southeast.
[a]Comparison among regions. [b]Comparison between Türkiye and regions.

between Türkiye in general and its regions (P = 0.522) (Table 2).

In 35% of the cases with PHPT, hypertension was present in the general area. This rate varied between 31% and 45% in different regions. However, no difference was observed between the regions or between the general country and regions with regard to hypertension (P > 0.05).

Of the cases operated due to PHPT in the university hospitals of Türkiye, 18.6% had a history of urolithiasis. The incidence of urolithiasis was significantly different between the regions (P < 0.001). The highest incidence belonged to the Mediterranean Region (44.7%), and the lowest incidence belonged to the Central Anatolian Region (14%). The incidence of urolithiasis was higher in the Mediterranean Region compared to Marmara, Aegean, Central Anatolia and East-Southeast Anatolia Regions (P < 0.001, P = 0.001, P < 0.001, and P < 0.001, respectively). The incidence in the Central Anatolian region was lower than that of the Marmara Region (P = 0.025). No other difference was observed between the regions. Compared to the general country, the incidence of urolithiasis was lower in the Central Anatolian region and higher in the Mediterranean Region (P = 0.043, P < 0.001, respectively) (Table 2).

Bone findings

The bone density findings of 688 out of 1,162 patients were present. In patients operated on due to PHPT in Türkiye, the rates of detection of abnormal findings (osteopenia or osteoporosis) in femur, vertebrae or radius with dual-energy X-ray absorbtiometry (DXA) were 67.6%, and 54% had osteoporosis (Table 3). The incidence of osteopororis in the regions except the Marmara Region was higher than the incidence of osteopenia. When the abnormal DXA findings of these cases were investigated, differences were observed between both the regions and the general country. The rates of patients with reduced bone mineralization in the Marmara and Mediterranean Regions were higher than that of Türkiye's general (P < 0.001 and P = 0.037, respectively). This rate was lower in the Central Anatolian Region than that of Türkiye's general region (P < 0.001). No significant difference was observed in the Aegean and East-Southeast Anatolian Regions compared to Türkiye's general region (P = 0.884 and P = 0.862, respectively). Differences were observed in the interregional comparisons with regard to the reduced bone mineralization rates. The Mediterranean and Marmara Regions had the highest rate of abnormal DXA findings. This rate was higher in the Marmara Region than Aegean, Central Anatolian and East-Southeast Regions (P = 0.003, P < 0.001, and P = 0.010, respectively). The lowest rate of abnormal bone density was observed in the Central Anatolian Region (39.5%). The differences were observed between the Central Anatolian Region and the Marmara, Mediterranean and East-Southeast Anatolian Regions (P < 0.001, P < 0.001, and P = 0.002, respectively). The highest rates of osteoporosis were observed in the Aegean (76.8%) and the Central Anatolian (68.5%) Regions.

The rate of patients with a history of bone fracture among those operated on due to PHPT in Türkiye was found to be 6%. When Türkiye's general region and the regions were compared, only the Central Anatolian Region had a higher bone fracture rate (11.6%) (P = 0.036). The interregional comparisons revealed significant differences in the frequency of patients with a history of bone fracture (P = 0.004). The rate of patients with a history of bone fracture was higher in the Central Anatolian Region than the Marmara (P = 0.019), Aegean (P = 0.039) and the East-Southeast Anatolian (P = 0.019) Regions, higher in the Mediterranean Region than the Aegean Region (P = 0.050), and higher in the Mediterranean Region than the East-Southeast Anatolian Region (P = 0.021) (Table 3).

The rate of bone cyst among patients operated on due to PHPT in Türkiye was found to be 1.5%. The interregional comparisons revealed a higher rate of bone cyst in the Central Anatolian Region than the Marmara Region (P < 0.001). No difference was observed between the remaining regions (Table 3).

Table 3. Bone findings in patients undergoing surgery for PHPT at university hospitals in Türkiye

Variable	Türkiye	Region					P-value[a]	P-value[b]
		1	2	3	4	5		
DXA								
Abnormal	465/688 (67.6)	269/328 (82)	69/101 (68.3)	20/22 (90.9)	73/185 (39.5)	34/52 (65.4)	<0.001	<0.001
Osteopenia	214 (46.0)	144 (53.5)	16 (23.2)	8 (40.0)	23 (31.5)	23 (67.6)	<0.001	<0.001
Osteoporosis	251 (54.0)	125 (46.5)	53 (76.8)	12 (60.0)	50 (68.5)	11 (32.4)		
Fracture	62/971 (6.0)	19/386 (4.7)	5/141 (3.4)	5/38 (11.6)	31/301 (9.3)	2/105 (6.0)	0.004	0.010
Bone cyst	14/943 (1.5)	1/422 (0.2)	1/132 (0.8)	0/41 (0)	10/243 (4.0)	2/105 (1.9)	0.003	0.009

Values are presented as number/N (%).
PHPT, primary hyperparathyroidism; DXA, dual-energy X-ray absorptiometry; N, total cases who have data related that parameter.
Regions: 1, Marmara; 2, Aegean; 3, Mediterranean; 4, Central Anatolia; 5, East-Southeast.
[a]Comparison among regions. [b]Comparison between Türkiye and regions.

Parathormone

The median PTH value in patients operated on in the university hospitals of Türkiye was found to be 220 pg/mL (range, 70–2,500 pg/mL). The regions with the highest and lowest median PTH values were the East-Southeast Anatolian Region (375 pg/mL) and the Mediterranean Region (180 pg/mL), respectively (Table 4). Differences were observed in the median PTH values between both Türkiye's general area and the regions, and between the regions (<0.001) (Tables 4, 5). The normal laboratory value of PTH was accepted as 35–68 pg/mL.

Calcium

The median serum total Ca^{+2} levels of the patients operated in the university hospitals of Türkiye was 11.2 mg/dL (range, 9.5–15.1 mg/mL). The Ca^{+2} value observed in all of the regions was 11 mg/dL or more. The region with the highest median Ca^{+2} value was the Mediterranean region (12.1 mg/dL). Differences were observed between both the Mediterranean Region and the other regions, and the Mediterranean Region and Türkiye's general region ($P < 0.05$) (Tables 4, 5). The median values of the remaining regions were closer to Türkiye's general region. The median values of Ca^{+2} in the 24-hour urine of the patients operated on due to PHPT in the university hospitals of Türkiye was 345 mg/24 hr (range, 40–1,385 mg/24 hr). No difference was observed between the regions ($P > 0.05$). The normal laboratory values for the total serum Ca^{+2} and urinary Ca^{+2} were accepted as 8.4–10.2 mg/dL and 100–300 mg/24 hr, respectively.

Phosphorus

The median serum phosphorus value in patients operated on due to PHPT in Türkiye was 2.4 mg/dL (range, 1–4.7 mg/dL). The regions with the lowest and highest median phosphorus values were the East-Southeast Anatolian and the Aegean Regions, respectively. Inter-regional differences were observed in the median phosphorus values ($P < 0.05$). The normal laboratory values of phosphorus was accepted as 2.3–4.7 mg/dL.

25-hydroxyvitamin D

The median value of 25(OH)D among patients operated on due to PHPT in Türkiye was 15 ng/mL (range, 3–98 ng/mL). The regions with the lowest median 25(OH)D level were the Marmara with 11 ng/mL (range, 4–98 ng/mL) and the East-Southeast Anatolian with 11 ng/mL (range, 3–24 ng/mL), whereas the region with the highest median 25(OH)D level was the Aegean Region with 31 ng/mL (range, 8–59 ng/mL) (Table 4). 25(OH)D deficiency was observed in 63% of the patients operated on due to PHPT in Türkiye's general region. The incidence of 25(OH)D deficiency was higher in the Marmara and the East-Southeast Anatolian Regions compared to Türkiye's general region ($P = 0.023$ and $P = 0.043$, respectively). The incidence of 25(OH)D deficiency was significantly lower in the Aegean, Mediterranean

Table 4. Laboratory findings in patients undergoing parathyroidectomy for PHPT at university hospitals in Türkiye

Variable	Türkiye	Region					P-value[a]	P-value[b]
		1	2	3	4	5		
PTH	220 (70–2,500)/1,162	236 (70–2,500)/434	225 (70–2,500)/150	180 (70–1,631)/67	192 (72–2,500)/396	375 (72–2,229)/115	<0.001	<0.001
Ca^{+2}	11.2 (9.5–15.1)/1,162	11 (9.6–15.1)/434	11.1 (9.5–15.5)/150	12.1 (9.6–17.6)/67	11.2 (9.5–16.8)396	11.2 (9.4–13.5)/115	<0.001	<0.001
P	2.4 (1–4.7)/991	2.3 (1.1–4.6)/327	2.6 (1.5–4.4)/127	2.4 (1.5–4.4)/64	2.5 (1–4.7)/372	2 (1.1–4.1)/101	<0.001	<0.001
$Ur.Ca^{+2}$	345 (40–1,385)/493	342 (49–980)/306	332 (40–1,385)/55	358 (43–772)/18	353 (41–1,300)/91	380 (150–754)/23	0.754	0.863
ALP	116 (10–299)/807	110 (47–1,682)/192	105 (33–2,772)/128	229 (48–1,567)/42	104 (22–2,128)/340	201 (10–2,990)/105	<0.001	<0.001
Vit D	15 (3–98)/331	11 (4–98)/201	31 (8–59)/11	29.5 (10–86)/22	21.4 (5–97)/75	11 (3–24)/22	<0.001	0.003
Low Vit D	207/331 (63)	145/201 (72)	3/11 (27)	6/22 (27)	34/75 (45)	19/22 (86)	<0.001	<0.001
High ALP	297/807 (37)	67/192 (35)	43/128 (34)	30/42 (71)	86/340 (25)	71/105 (68)	<0.001	<0.001

Values are presented as median (range)/N or number/N (%).
PHPT, primary hyperparathyroidism; N, total cases who have data on that parameter.
Regions: 1, Marmara; 2, Aegean; 3, Mediterranean; 4, Central Anatolia; 5, East-Southeast.
PTH, parathormon (35–68 pg/mL); Ca^{+2}, calcium (8.4–10.2 mg/dL); P, phosphorus (2.3–4.7 mg/dL); ALP, 25–100 U/L; Low Vit D, 25–(OH) Vitamin D ≤ 20 ng/mL); $Ur.Ca^{+2}$, Urine Ca^{+2}(100–300 mg/24 hr).
[a]Comparison among regions. [b]Comparison between Türkiye and regions.

Table 5. P-values of comparisons for laboratory data among regions in Türkiye

Regions	Vit D	Urine Ca^{+2}	PTH	Ca^{+2}	P	ALP
1–2	0.001	0.431	0.705	0.434	0.001	0.927
1–3	<0.001	0.487	0.008	<0.001	0.243	<0.001
1–4	<0.001	0.556	0.002	0.861	0.008	0.172
1–5	0.278	0.298	<0.001	0.196	0.002	<0.001
2–3	0.749	0.903	0.054	<0.001	0.162	<0.001
2–4	0.032	0.721	0.103	0.401	0.228	0.276
2–5	<0.001	0.831	<0.001	0.610	<0.001	<0.001
3–4	0.011	0.689	0.376	<0.001	0.604	<0.001
3–5	<0.001	0.979	<0.001	<0.001	0.002	0.490
4–5	<0.001	0.624	<0.001	0.171	<0.001	<0.001

PTH, parathormone; Ca^{+2}, calcium; Vit, vitamin; P, phosphorus.
Regions: 1, Marmara; 2, Aegean; 3, Mediterranean; 4, Central Anatolia; 5, East-Southeast.

Table 6. Operative findings in patients undergoing parathyroidectomy for PHPT at university hospitals in Türkiye

Variable	Türkiye	Region					P-value[a]	P-value[b]
		1	2	3	4	5		
Adenom								
Single	1,028/1,146 (90)	377/431 (87)	136/146 (93)	59/66 (89)	353/388 (91)	103/115 (90)	>0.05	>0.05
Multiple	103/1,146 (9)	51/431 (12)	10/146 (7)	7/66 (11)	23/388 (6)	12/115 (10)	>0.05	>0.05
Hyperplasia	15/1,146 (1)	3/431 (1)	0/146 (0)	0/66 (0)	12/388 (3)	0/115 (0)	>0.05	>0.05
Dimention (mm)	16 (4–70)/928	16.5 (4–70)/394	20 (6–60)/118	15 (7–65)/61	15 (5–65)/249	20 (7–40)/106	<0.001	<0.001
Thyroidectomy[c]	342/958 (36)	88/277 (32)	49/108 (45)	22/67 (33)	134/391 (34)	49/115 (43)	>0.05	>0.05

Values are presented as number/N (%) or median (range)/N.
PHPT, primary hyperparathyroidism; N, total cases who have data on that parameter.
Regions: 1, Marmara; 2, Aegean; 3, Mediterranean; 4, Central Anatolia; 5, East-Southeast.
[a]Comparison among regions. [b]Comparison between Türkiye and regions. [c]Thyroidectomy means concurrent thyroidectomy.

and Central Anatolian Regions compared to Türkiye's general region (P = 0.026, P = 0.002, and P = 0.006, respectively). A blood level of 25(OH)D ≤ 20 ng/mL was accepted as 25(OH)D deficiency in this study.

The number of patients with 25(OH)D deficiency was significantly different between the regions (P < 0.001). 25(OH)D deficieny was observed in the Aegean and the Mediterranean Regions with the lowest rate (Table 4). The East-Southeast Anatolian (86%) and the Marmara (72%) Regions were the regions with highest rates of 25(OH)D deficiency. 25(OH)D deficiency was higher in the Marmara Region compared to the Aegean, Mediterranean and Central Anatolian Regions (P = 0.004, P < 0.001, and P < 0.001, respectively). No difference was observed between the Marmara and the East-Southeast Anatolian Regions (P = 0.237). The incidence of 25(OH)D deficiency was higher in the East-Southeast Anatolian Regions compared to the Aegean, Mediterranean and the Central Anatolian Regions (P = 0.001, P < 0.001, and P = 0.002, respectively). No difference was observed between the Aegean Region and the Mediterranean and Central Anatolian Regions (P = 0.338 and P = 1.000, respectively). No difference was observed between the Central Anatolian and the Mediterranean Regions (P = 0.205) (Table 4).

Alkaline phosphatase

The median level of ALP among patients operated due to PHPT in the university hospitals of Türkiye was determined to be 116 U/L (range, 10–299 U/L). Regions with the highest median ALP levels were the Mediterranean (229 U/L; range, 48–1,567 U/L) and the East-Southeast Anatolian (201 U/L; range, 10–2,990 U/L) Regions. The ALP levels observed in these 2 regions were significantly higher compared to the remaining regions (P < 0.05). The ALP levels were found to be higher than the normal level in 37% of the patients operated in Türkiye's general region. The number of cases with an ALP level higher than normal was highest in the East-Southeast Anatolian (68%) and the Mediterranean (71%) Regions (Tables 4, 5). The normal laboratory values of ALP was accepted as 25–100 U/L.

Operative findings

The rates of single adenoma, multiple adenoma and hyperplasia in patients operated on due to PHPT in the university

hospitals of Türkiye were 90%, 9%, and 1%, respectively. No difference was observed between the regions ($P > 0.05$) (Table 6). The median adenoma size in the longest axis was 16 mm (range, 4–70 mm). Regions with the largest adenoma size were the Aegean (20 mm; range, 6–60 mm) and the East-Southeast Anatolian (20 mm; range, 7–40 mm) Regions. The median adenoma sizes observed in these 2 regions were higher than those of the Mediterranean and Central Anatolian Regions ($P < 0.001$). No statistical difference was observed between Türkiye's general area and the regions ($P > 0.05$). Concomitamt thyroidectomy was performed for 36% of the patients undergoing the PHPT operation for different reasons. No difference was observed between the regions with regard to concomitant thyroidectomy ($P > 0.05$).

DISCUSSION

The age of patients with PHPT is greater in Western Countries (USA, 60–62; Germany, 59; Italy, 59; Denmark, 65) than Eastern countries (China, 37; India, 38) [1,6-11]. In this study, the median age of patients with PHPT was 52. This indicates that the age of the patients with PHPT in Türkiye is somewhere between Eastern and Western countries. When the regions were investigated, the median age of the patients in the East-Southeast Anatolian Region was significantly younger than those of the remaining regions, except for the Mediterranean Region. Griebeler et al. [6] reported that the median age of the cases in Rochester, America with PHPT was 55 between 1985 and 1997, which significantly increased by time reaching 60 between 1998 and 2010. Similarly, in studies conducted in China and Hong Kong, the mean age of the patients with PHPT had increased in time compared to the previous times [12,13]. Another characteristic concerning age was that the patients living in regions with a severe form of the disease were younger [1,11]. However, it was reported in age and sex matched studies that the clinical and laboratory findings of the disease may be different [3,4]. There are not many studies investigating the factors affecting the difference in age of patients in different countries or regions of a country.

With the use of autoanalysers in the 1970s, a significant increase was reported in both the incidence of the cases with PHPT and the rate of the asymptomatic cases related to the frequent measurement of routine Ca^{++} [14,15]. This change is specifically significant in Western countries including North America and North Europe. In the remaining regions of the world, the number of classic symptomatic PHPT cases is still high despite a partial change [12,16]. For example, the rates of kidney stone among patients with PHPT are 3%–20% in USA, 11% in Germany, 42% in China, and 50% in India [1,8,17,18]. In this study, the kidney stone rate in Türkiye was found to be 18%. Interregional comparisons have shown that this rate differed between 14% and 44%. The region with the highest incidence of kidney stone was the Mediterranean Region. Mollerup et al. [19] have reported that kidney stone was more common among young patients. The Mediterranean Region included the second youngest patient group after the East-Southeast Anatolian Region, although not significantly different from the other regions. However, although the ages of patients in Türkiye were younger compared to the Western countries, and those in the East-Southeast Anatolian Region were younger than the other regions, no significant difference was observed with regard to the rates of urolithiasis. The differences observed in the urolithiasis rates between the regions/countries may be related to the different etiological factors in kidney stone formation or ineffective radiological evaluation of the kidneys in asymptomatic patients [20-22].

The bony findings in patients with PHPT may differ between countries/regions. For example, the bone mineral density in caucasian women with PHPT living in the USA were found to be higher than those living in Italy [4]. Bone diseases among patients with PHPT have been reported to vary between 5% and 8% in the USA [17]. The rate of osteoporosis was 100% in China and 50% in Taiwan [1,23]. Bone cyst has been reported in each case in India [11]. In this study, bone diseases (osteopenia or osteoporosis) were detected in 67% of the cases with PHPT. However, when the regions of Türkiye were investigated separately, it was observed that the rates of bone disease were homogeneous. Furthermore, the rates of bone diseases in the Mediterranean (90%) and the Marmara (82%) Regions were much higher than the mean of Türkiye. According to these data, it may be concluded that the rate of bone diseases in Türkiye is somewhere between the eastern and western countries, but rather similar to the eastern countries in some regions.

It has been believed that 25(OH)D deficiency has an important role in different severities of PHPT observed among the world. In regions where 25(OH)D deficiency is endemic, a severe form of the disease is observed, whereas mostly the asymptomatic form is observed in western counties [24]. It has been reported that 25(OH)D deficiency is an important factor defining in particular the bone disease in patients with PHPT [9,10,24,25]. Furthermore, a negative correlation is present between 25(OH)D levels and the adenoma weight, and a positive correlation with PTH, Ca^{++} and ALP levels [7,19,24-26]. In this study, the East-Southeast Anatolian Region and the Marmara Region were the regions with more frequent patients with 25(OH)D deficiency and with more severe PHPT. However, the rate of patients with subnormal 25(OH)D levels has been reported as 63% in Türkiye, 93% in France, 81% in Denmark, 33% in Italy, and 86% in China [10,12,26]. When these rates are investigated, it is obvious that it is not possible to explain the more severe form of the disease observed in eastern countries, and the asymptomatic form observed in western countries with

25(OH)D deficiency only. Additionally, Mishra et al. [11] claimed that 25(OH)D levels were normal despite the severe form of the disease in patients with PHPT in India, and thus, additional pathogenetic factors may be present in the formation of the severe disease. Likewise, although the number of patients with 25(OH)D deficiency in the Mediterranean Region of Türkiye was quite low, this region had the highest rates of urolithiasis, bone diseases, blood Ca^{+2} and ALP levels. Therefore, it should be considered that Vitamin D is not the only factor indicating the severity of PHPT, delays in access to detection and treatment of the disease, and factors such as ethnicity, genetics, and race may play a defining role in the severity of the disease as well [2,6,27-29].

The median PTH and Ca^{+2} levels in patients with PHPT in Türkiye were found to be 220 pg/mL and 11.2 mg/dL, respectively. The median Ca^{+2} in USA was reported to be 10.8 mg/dL [6]. The median PTH and Ca^{+2} levels were 134 pg/mL and 11.4 mg/dL in France, 102 pg/mL and 11 mg/dL in Denmark, and 141 pg/mL and 11.1 mg/dL in Italy, respectively [9,10,26]. The PTH levels were 20 and 17 fold the normal value in China and India, respectively [1,11]. In another study from Korea, mean PTH and Ca^{+2} levels were reported as 263 pg/mL and 11.6 mg/dL, respectively [30]. According to these data, no significant difference is observed between the blood Ca^{+2} levels of the patients with PHPT in Türkiye and Europe and America; however, the PTH levels were higher than those in western countries.

The limitations of this study were: it was retrospective, there was a lot of data loss, lower possibilities of interlaboratory differences, and the data of the study were old. Due to the difficulty of data collection, recent data could not be added. However, the data of patients operated on due to PHPT in Türkiye's general and separate regions is not available in the literature. We believe that we have contributed to literature in this regard.

In this study, the general characteristics of patients with PHPT have been determined, and it has been demonstrated that the demographic, clinical and laboratory data of cases living in different regions of the same country may not be homogenous. As it is known, the patients' clinical characteristics are under the influence of multiple factors such as ethnic, genetic and socio-economic statuses, nutritional habits (for example, milk consumption), climatic conditions, and the duration of living in the region in question. Furthermore, due to the fact that this study was retrospective, it has not been possible to evaluate the regional differences due to insufficiency of data. In order not to be speculative, no comment has been made regarding regional differences..

In conclusion, the clinical and laboratory characteristics of the patients operated due to PHPT in different classically defined geographical regions of Türkiye differ. Furthermore, the general findings of the cases in Türkiye give us a hint that the severity of the disease here is somehwere between Eastern and Western countries. This study indicates that the clinical presentation of PHPT may vary even in different regions of the same country. Therefore, it should be considered when planning such studies comparing the differences between regions/countries.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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