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ORIGINAL RESEARCH

Identifying Clinical Characteristics of Hypoparathyroidism in Turkey: HIPOPARATURK-NET Study

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Abstract

Hypoparathyroidism is an orphan disease with ill-defined epidemiology that is subject to geographic variability. We conducted this study to assess the demographics, etiologic distribution, treatment patterns and complication frequency of patients with chronic hypoparathyroidism in Turkey. This is a retrospective, cross-sectional database study, with collaboration of 30 endocrinology centers located in 20 cities across seven geographical regions of Turkey. A total of 830 adults (mean age 49.6 ± 13.5 years; female 81.2%) with hypoparathyroidism (mean duration 9.7 ± 9.0 years) were included in the final analysis. Hypoparathyroidism was predominantly surgery-induced ($n = 686$, 82.6%). The insulting surgeries was carried out mostly due to benign causes in postsurgical group (SG) ($n = 504$, 73.5%) while patients in nonsurgical group (NSG) was most frequently classified as idiopathic ($n = 103$, 71.5%). The treatment was highly dependent on calcium salts ($n = 771$, 92.9%), calcitriol ($n = 786$, 94.7%) and to a lower extent cholecalciferol use ($n = 635$, 76.5%) while the rate of parathyroid hormone ($n = 2$, 0.2%) use was low. Serum calcium levels were most frequently kept in the normal range (sCa 8.5–10.5 mg/dL, $n = 383$, 46.1%) which might be higher than desired for this patient group. NSG had a lower mean plasma PTH concentration (6.42 ± 5.53 vs. 9.09 ± 7.08 ng/l, $p < 0.0001$), higher daily intake of elementary calcium (2038 ± 1214 vs. 1846 ± 1355 mg/day, $p = 0.0193$) and calcitriol (0.78 ± 0.39 vs. 0.69 ± 0.38 mcg/day, $p = 0.0057$), a higher rate of chronic renal disease (9.7% vs. 3.6%, $p = 0.0017$), epilepsy (6.3% vs. 1.6%, $p = 0.0009$), intracranial calcifications (11.8% vs. 7.3%, $p < 0.0001$) and cataracts (22.2% vs. 13.7%, $p = 0.0096$) compared to SG. In conclusion, postsurgical hypoparathyroidism is the dominant etiology of hypoparathyroidism in Turkey while the nonsurgical patients have a higher disease burden with greater need for medications and increased risk of complications than the postsurgical patients.

Keywords Hypoparathyroidism · Hypocalcemia · Epidemiology · Turkey · Parathyroid hormone

Introduction

Hypoparathyroidism is a rare endocrine disorder characterized by hypocalcemia due to inadequate parathyroid hormone (PTH) secretion [1]. In nearly 75% of cases, accidental damage to the parathyroid glands as a complication of neck surgery is the source of compromised PTH secretion [2]. Postsurgical hypoparathyroidism is mostly transient and resolve in 6 months while hypoparathyroidism that extends over 6 months after the insulting surgery is defined as chronic. Depending on the experience of the surgeon and the extent of surgery, transient hypoparathyroidism occur in 25.4–83%, whereas chronic hypoparathyroidism occur in 0.12–4.6% of the cases [3]. More invasive procedures, such as total thyroidectomy or extensive cancer surgery, increases the risk further for both transient and permanent hypoparathyroidism [4]. Hypoparathyroidism that is unrelated to surgery occurs in 25% of the patients and is caused

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by autoimmunity, conditions associated with infiltration of the parathyroid gland and rare genetic disorders as DiGeorge syndrome [5]. Hypoparathyroidism can occur in the absence of a clear etiology. These patients are most likely suffering from an autoimmune form of the disease [4]. Following a careful exclusion of all the possible causes of hypoparathyroidism, these cases may then be categorized as idiopathic hypoparathyroidism [6].

The conventional treatment involves replacement of the missing calcium, aiming to restore serum calcium levels. Large doses of calcium salts and active vitamin D are used for that purpose. However, it is challenging to keep serum calcium steady while balancing it to the hyperphosphatemia that frequently develops due to insufficient PTH action. Even when the serum calcium levels are in the target range, patients may experience hypercalciuria due to the high load of calcium filtered by the kidney, increasing the risk of nephrolithiasis and renal dysfunction. Formation of calcium–phosphate salts in soft tissues, mainly the kidney, basal ganglia and lens [7] lead to long-term complications translated as renal stones and impairment, neuropsychiatric diseases and cataracts that might be unavoidable in the long term [8]. There are also some non-classical risks attributed to hypoparathyroidism such as increased risk of cardiovascular disease, arrythmias and recurrent infections [9]. The course of disease is further complicated by higher rates of hospital stays and emergency service visits and a possibly a higher risk of mortality [10, 11].

Quantifying the prevalence of hypoparathyroidism has been challenging historically, due to the rarity of the condition and its variable presentation. Over the last decade, population or registry-based studies from various countries have helped us better understand the epidemiology of hypoparathyroidism. Currently, the estimated prevalence of this disorder has been reported to range between 10.1 and 40.0 per 100,000 people [3]. However, substantial geographic variability was evident in those studies regarding the etiological distributions, complication rates and treatment trends.

To date, no study has been performed investigating aforementioned parameters in hypoparathyroidism patients in Turkey. In this study, we aimed to evaluate the clinical and demographical parameters, the etiologic factors, treatment patterns and rates of short and long-term morbidities associated with hypoparathyroidism followed up at endocrinology clinics in Turkey.

Materials and Methods

Study Design

This multicentric study was organized as a collective effort by the "Metabolic Bone Diseases Workgroup" of "Turkish Society of Endocrinology and Metabolism". An invitation was sent to all tertiary endocrinology clinics in Turkey to complete a survey regarding patients with permanent hypoparathyroidism. The centers willing to participate were sent a detailed data sheet, which were filled retrospectively by endocrinologists through a detailed review of their patient records, including clinical notes, hospital discharge summaries and laboratory results. Overall, 30 endocrinology clinics, based in 20 cities distributed over seven geographical regions of Turkey responded to the invitation. Geographic regions were represented in a nonhomogeneous manner due to the distribution of tertiary endocrinology centers throughout Turkey (Marmara 31.1%, Central Anatolia 26.9%, Aegean 13.1%, Eastern Anatolia 12.0%, Southeastern Anatolia 8.0%, Mediterranean 4.6%, Black Sea 4.3%). The patient inclusion period was from November 2018 through January 2020.

Patient Selection

Patients were retrieved from the corresponding hospital databases using the ICD-10 codes: "E20.0 (Idiopathic hypoparathyroidism)", "E20.8 (Other hypoparathyroidism)", "E20.9 (Hypoparathyroidism, unspecified)", "E89.2 (Postprocedural hypoparathyroidism)", "E83.51 (hypocalcemia)". The diagnosis of chronic permanent hypoparathyroidism was confirmed by the physicians through medical reports and patients were eligible only if they had at least one recorded inappropriately low-plasma PTH level in the setting of hypocalcemia (calcium concentration below the lower limit of normal), necessitating continuous treatment with supplemental calcium and/or active vitamin D for more than 6 months to maintain serum calcium (sCa) in the low-normal range. Pediatric patients (under 18 years old) were not included.

A total of 1005 patients' data were returned and all data were reviewed by two authors (D.G.Y and C.K.D) to make sure the patient met the inclusion criteria. Patients with equivocal or missing data related to patient inclusion criteria (patients with hypoparathyroidism lasting less than 6 months, patients without documented hypocalcemia, patients who had low sCa levels with a serum PTH > 20 ng/l, patients with missing sCa and PTH levels, patients with pseudohypoparathyroidism) were excluded from the data set and the final cohort included 830 patients.

Parameters of Interest

The data set covered distinct topic areas of (1) *demographics* (gender, date of birth, literacy level, BMI); (2) *medical follow-up patterns* (duration and frequency of follow-up at the corresponding center); (3) *diagnosis* [age of disease onset, clinical setting at disease onset, type of chronic

hypoparathyroidism (postsurgical or nonsurgical), type and indication of surgery in case of postsurgical hypoparathyroidism, etiology/presence of polyglandular involvement/family history in the case of nonsurgical hypoparathyroidism]; (4) *current management* [information on the use of calcium supplements (including prescription formulations and over-the-counter supplements, total daily calcium intake was calculated as the sum of all calcium sources), active vitamin D preparations, cholecalciferol, thiazides or recombinant PTH with daily doses and brand names], (5) *biochemical evaluations* [most recent results for sCa, phosphate (sP), creatinine, albumin, magnesium, 25 (OH)D, ALP, urinary calcium and creatinine, sCa 6 and 12 months before the current visit, lowest and highest levels of sCa and sP recorded during long-term follow-up (sCa were corrected for albumin concentration), lowest PTH recorded following the diagnosis (autoanalyzer platforms used for biochemical parameters, 25 (OH)D measured by HPLC or chemiluminescence immunoassays, intact PTH measured by chemiluminescence immunoassays)], (6) *radiological evaluation* [bone mineral density measured using dual-energy X-ray absorptiometry (DXA), radiological reports including renal/abdominal ultrasounds, abdominal computed tomography (CT) scans, and head CT scans], (6) history of hypocalcemia or hypercalcemia requiring medical assistance [hypocalcemia defined as sCa < 8 mg/dL and hypercalcemia as > 10.5 mg/dL documented by hospital records in the (1) "last 1 year" and (2) since the diagnosis of hypoparathyroidism "all-time hypo/hypercalcemia"]; (7) *long-term complications that are attributed to hypoparathyroidism* [Definitions-nephrolithiasis: history or radiological presence of renal stones, nephrocalcinosis: radiological presence of nephrocalcinosis, chronic renal disease: estimated creatinine clearance levels in the last 12 months or undergoing renal replacement therapy, ischemic heart disease: history of myocardial infraction or angiographical presence of coronary disease, arrhythmia: history or current use of antiarrhythmic drugs or medical record with demonstration of arrhythmia, ischemic cerebrovascular disease: history of cerebrovascular event or angiographical presence of cerebrovascular disease, epilepsy: history or current use of antiepileptics for seizures, parkinsonism: history or current use of medications for the management of parkinsonism, psychiatric disease: history or current use of antidepressants or antipsychotics, cataracts: medical record of an ophthalmologist or history of cataracts surgery, increased frequency of infections: more than 3 episodes of any recorded infection and (8) *medical comorbidities* (presence of malignancy, presence of osteoporosis, age of menopause, history or current use of antiresorptive drugs, history of fragility fractures, alcohol or smoking habits).

Statistics

Descriptive statistics were presented as mean and standard deviation (SD) for continuous variables and counts and percentages for categorical variables. Categorical data were analyzed using the Chi-square (χ^2) test. The Mann–Whitney test was used for the continuous variables. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism version 9.0.0 for Mac OS.

Results

Overall, 830 patients were included in the final analysis. Table 1 depicts the baseline characteristics of these patients. The mean age of the patients at the time of evaluation was 49.6 ± 13.5 years, and the majority of the patient population were women (81.2%). The mean duration of disease was 9.7 ± 9.0 years with an average age at diagnosis of 38.9 ± 14.5 years. Time from first admission to the referring center to study inclusion was more than 5 years in 364 (44.2%), more than 1 year in 300 (36.4%), more than 6 months in 64 (7.8%) and less than 6 months in 40 (4.8%). In 56 (6.8%), the current evaluation was their first admission to the corresponding center. 205 (26.1%) of the patients had been followed up more frequently than every 3 months, 351 (44.7%) every 3–6 months, 138 (17.6%), every 6–12 months, 74 (9.4%) less frequently than once a year and in 18 (2.2%) the frequency of follow-up was unidentified. The median frequency of sCa observations was 4 times per year (IQR 2–6). Of all patients, 132 (15.9%) had sCa measurements < 7.5 mg/dL, 121 (14.6%) between 7.5 and 8.0 mg/dL, 185 (22.3%) between 8.0 and 8.5 mg/dL, 383 (46.1%) between 8.5 and 10.5 mg/dL and 9 (1.1%) > 10.5 mg/dL under their current treatment. The mean calcium phosphate product was 38.02 ± 8.47, with 12 patients having values over 55 mg^2/dL^2. The mean all-time-low sCa levels extracted from the referring center's patient records was 6.8 ± 1.1 mg/dL and the all-time-high calcium levels were 9.6 ± 1.2 mg/dL. Similarly, the mean all-time-high sP levels were 5.7 ± 1.1 mg/dL, and the mean lowest sP levels were 3.9 ± 1.0 mg/dL. Three hundred and seventy of the patients had been hospitalized at least once for hypocalcemia since they had been diagnosed with hypoparathyroidism and 215 patients had at least one episode of hypocalcemia in the last year that required medical assistance. 70 patients experienced hypercalcemia at least once due to treatment after the diagnosis and there were 33 patients who developed hypercalcemia in the last year. There were 255 patients with all three point (current, measured 6 and 12 months ago) sCa levels in the normal range.

The majority of the cases (82.6%) developed hypoparathyroidism due to a surgical procedure. The most frequent

Table 1 Summary of demographics, etiology and clinical characteristics of hypoparathyroidism patients in the HIPOPARATURK-NET study

	Total ($n=830$)
Age, years	49.6 ± 13.5
Gender (F/M), *n* (%)	674/156 (81.2/18.8)
BMI, kg/m^2	28.8 ± 6.0
Duration of disease, years(range)	9.7 ± 9.0 (1–61)
Hypoparathyroidism etiology, *n* (%)	
Postsurgery, *n* (%)	**686 (82.6)**
NG/MNG (euthyroid)	296 (43.2)
NG/MNG (toxic)	115 (16.8)
Graves disease	62 (9.0)
Thyroid cancer	182 (26.5)
Parathyroid surgery	23 (3.3)
Other neck surgery	8 (1.2)
Nonsurgical, *n* (%)	**144 (17.4)**
Idiopathic	103(71.5)
Autoimmune (APS)	35 (24.3)
DiGeorge syndrome	4 (2.8)
Thalassemia related	2 (1.4)
Type of initial presentation, *n* (%)	
Postsurgical	646 (77.8)
Emergency admission due to tetany	20 (2.4)
Outpatient with symptoms of paresthesia/latent tetany	109 (13.1)
Asymptomatic and diagnosed during screening	17 (2.0)
Diagnosed in childhood	25 (3.0)
Other	13 (1.7)
Medical comorbidities, *n* (%)	734 (88.4)
Hypothyroidism	612 (73.7)
Hypertension	181 (21.8)
Hyperlipidemia	75 (9.0)
Dementia	3 (0.4)
T2DM	94 (11.3)
T1DM	2 (0.2)
Osteoporosis	47 (5.7)

BMI body mass index, *NG* nodular goiter, *MNG* multinodular goiter, *APS* autoimmune polyglandular syndrome, *T2DM* type 2 diabetes mellitus, *T1DM* type 1 diabetes mellitus

type of surgery was thyroidectomy due to euthyroid nodular or multinodular goiter that ultimately turned out to be benign (43.2%) or thyroid cancer (26.5%) histopathologically. Surgery was indicated for toxic nodular/multinodular goiter in 16.8% and Graves' disease in 9%. Parathyroidectomies for the treatment of hyperparathyroidism made up 3.3% of the postsurgical cohort. Two patients had simultaneous thyroidectomy and parathyroidectomy, and six had laryngectomy with neck dissection due to larynx cancer, classified as other type of surgery (Table 1). There were 144 patients with nonsurgical hypoparathyroidism. Most of those patients were classified as idiopathic ($n=103$, 71.5%) while 35 (24.3%) had autoimmune-mediated hypoparathyroidism as part of autoimmune polyglandular syndrome, 4 (2.8%) patients had DiGeorge syndrome and 2 (1.4%) patients had transfusion-related hypoparathyroidism due to beta-thalassemia major (Table 1).

There was a significantly higher female predominance in the postsurgical group (SG) (86.0%) compared to nonsurgical group (NSG) (58.3%) ($p<0.0001$). The two groups did not differ in terms of disease duration ($p=0.8593$). The mean plasma PTH of the NSG was lower than the SG (6.42 ± 5.53 vs. 9.09 ± 7.08, $p<0.0001$) while current sCa ($p=0.8591$) and sP ($p=0.7310$) levels under treatment were similar. The NSG had a lower mean all-time low sCa (6.4 ± 1.2 vs. 6.9 ± 1.0 mg/dL, $p<0.0001$) and a higher mean all-time-high sP (6.0 ± 1.4 vs. 5.7 ± 1.0 mg/dL, $p=0.0012$) levels than the SG. The rates of "all-time" [SG 295 (43.0%) vs. NSG 75 (52.1%), $p=0.0527$] and "last one year" [SG 178 (25.9%) vs. 37 (25.7%), $p>0.9999$] hypocalcemia

episodes were similar for SG and NSG. NSG had a higher rate of hypercalcemic episodes compared to SG in terms of "all time hypercalcemia" [SG 51 (7.4%) vs. NSG 19 (13.2%), $p=0.0312$] and "hypercalcemia in the last year" [SG 21 (3.1%) vs. 12 (8.3%), $p=0.0077$].

Table 2 summarizes the patients' current medications for the management of hypoparathyroidism. Overall, 771 (92.9%) of the patients in the cohort used at least one type of calcium preparation. The most frequently used calcium formulation was calcium carbonate combined with cholecalciferol used by 68.6% of the cohort whereas calcium carbonate (as tablet or powder) was used by 16.4% and acetate (as tablet) by 8.0%. The mean elementary calcium dose was significantly higher in NSG than SG ($p=0.0193$). The non-calcium using patients in the cohort were managed with calcitriol alone. Overall, 786 (94.7%) of the patients used calcitriol and the calcitriol dose needed by the NSG (0.78 ± 0.39 mcg/day) was significantly higher than the SG (0.69 ± 0.38, $p=0.0057$). Cholecalciferol was used mainly in a combined fashion with calcium carbonate (68.6% of the patients), and only 8.0% of the patients received cholecalciferol as drops, with similar doses for SG and NSG. Cholecalciferol was used concurrently with calcitriol in 561 (67.6%) patients. Magnesium supplementation (5.5%) and thiazides (7.2%) were taken by a small number of patients in the cohort, and only two patients received teriparatide (rPTH 1–34) 20 mcg/day for the management of difficult to control calcium levels (Table 2).

The chronic complications that are attributed to hypoparathyroidism are summarized in Table 2. Nephrolithiasis was reported in 8.0% and nephrocalcinosis in 0.7% of the patients with similar rates between SG and NSG. Of 830 patients, urinary calcium excretion was measured in 298 (35.9%) patients and the mean 24 h urinary excretion of calcium was 209.6 ± 198.9 mg. The urinary calcium excretion was not related to the presence of nephrolithiasis in our cohort ($p=0.475$). Serum creatinine levels were higher and chronic renal disease was more frequent in the NSG compared to SG (Table 2). Cranial imaging was undertaken in 234 (28.2%) of the patients, and intracranial calcifications were detected in 34 (4.1%), most commonly involving the basal ganglia. There was a higher rate of seizures ($p=0.0009$) and intracerebral calcification presence (<0.0001) in the NSG than the SG, whereas cerebrovascular event ($p=0.0959$) and parkinsonism (0.2029) rates were similar. Psychiatric disease rate had a higher trend in the NSG that did not reach statistical significance ($p=0.0705$). Cataracts was the most frequent complication associated with hypoparathyroidism in this cohort, reaching a rate of 15.2% and was more frequent in the NSG (22.2% vs. 13.7%, $p=0.0096$). Serum calcium levels were lower in patients with increased frequency of infections (8.14 ± 0.85 vs. 8.36 ± 0.94 mg/dL, $p=0.020$) and higher in patients with epilepsy (9.00 ± 0.65 vs. 8.34 ± 0.93 mg/dL, $p<0.001$) while sCa was not related to the presence of intracranial calcifications ($p=0.588$) or parkinsonism ($p=0.877$) as well as other long-term complications as nephrolithiasis ($p=0.347$), nephrocalcinosis ($p=0.938$), chronic renal disease ($p=0.095$), ischemic heart disease ($p=0.535$), arrhythmia ($p=0.628$), ischemic cerebrovascular disease ($p=0.535$) and cataracts ($p=0.160$).

Dual-energy X-ray absorptiometry (DXA) was performed on 308 (37.1%) patients. Lumber and femoral neck densities, t and z scores were similar between SG and NSG (Table 2) and women and men (Table 3). Thirty-six fractures were reported, with 21 patients having history of bisphosphonate. There were 17 (47.2%) lower extremity fractures (including hip fractures), 8 (22.2%) upper extremity fractures, 5 (13.9%) vertebral fractures, and 6 (16.7%) fractures where the site of fracture was not specified. There were 312 postmenopausal women (mean age at menopause 46.5 ± 6.0 years) and 334 premenopausal women in the study, 111 of whom got pregnant after the diagnosis of hypoparathyroidism, resulting in 98 healthy infants, 36 aborted pregnancies and six current pregnancies.

Discussion

This is the first study investigating etiology, clinical and biochemical characteristics, treatment regimens and complications of hypoparathyroidism in Turkey. Our results showed that the predominant cause of hypoparathyroidism is surgery-related similar to the previous publications in the literature. However, the rate of surgical hypoparathyroidism is on the higher end in our cohort (82.6% vs. 66.0–82.5%) [10, 12–15] and the rate of cancer surgery is lower (less than a third of postsurgical patients) than the rates reported previously [10, 15]. We suppose that there is a trend for surgeons in Turkey to treat benign thyroid diseases with surgery more often than what is practiced in US and other European countries. Limited data suggest that up to 90% of thyroidectomies are done for benign thyroid diseases in Turkey [16, 17]. Such approach represents the surgical trends over the last 20 years in Turkey and might be explained by the surgical training provided to practitioners, the rate of guideline follow-up in treatment choices, limited number of high-volume endocrine surgeons in Turkey and the strain placed on surgeons by the performance-based payment system in Turkey, which might be driving up surgery rates. Our study confirms that both the rate and etiology of postsurgical hypoparathyroidism is a reflection of the geographical differences in thyroid surgery practices.

Nonsurgical cases constituted 17.4% of our cohort and majority were classified as idiopathic (71.5%). Genetic testing was very limited and available for 4 (2.8%) cases with

Table 2 Demographic and laboratory characteristics, medications used and complications reported in hypoparathyroidism patients according to etiology

	Total ($n=830$)	Surgical hypoparathyroidism ($n=686$)	Nonsurgical hypoparathyroidism ($n=144$)	p*
Age, years	49.6 ± 13.5	50.3 ± 12.9	46.5 ± 15.9	**0.0075**
Gender (F/M), *n* (%)	674/156 (81.2/18.8)	590/96 (86.0/14.0)	84/60 (58.3/41.7)	**< 0.0001**
BMI, kg/m^2	28.8 ± 6.0	29.1 ± 5.9	27.3 ± 6.1	**0.0002**
Duration of disease, years	9.7 ± 9.0	9.7 ± 9.2	9.4 ± 8.1	0.8593
PTH, ng/L (15.0–65.0)**	8.63 ± 6.91	9.09 ± 7.08	6.42 ± 5.53	**< 0.0001**
sCa, mg/dL (8.5–10.5)	8.34 ± 0.94	8.35 ± 0.93	8.34 ± 1.02	0.8591
sP, mg/dL (2.3–4.7)	4.79 ± 3.41	4.81 ± 3.72	4.74 ± 0.97	0.7310
sCre, mg/dL (0.6–1.3)	0.83 ± 0.43	0.81 ± 0.44	0.91 ± 0.38	**< 0.0001**
sAlb, g/dL (3.4–4.8)	4.29 ± 0.39	4.30 ± 0.38	4.28 ± 0.42	0.9556
sMg, mg/dL (1.7–2.2)	1.74 ± 0.40	1.73 ± 0.38	1.78 ± 0.49	0.3181
s25(OH)D, ng/mL (6.2–45.5)	26.14 ± 12.32	25.19 ± 11.57	30.66 ± 14.58	**< 0.0001**
sALP, IU/L (40–150)	70.5 ± 38.4	69.4 ± 27.8	76.0 ± 69.6	0.3742
BMD	$n=308$	$n=250$	$n=58$	
Lumber				
g/cm^2	1.141 ± 0.243	1.136 ± 0.229	1.159 ± 0.295	0.3440
T score	0.447 ± 1.817	0.379 ± 1.803	0.768 ± 1.902	0.2575
Z score	1.040 ± 1.709	0.965 ± 1.673	1.379 ± 1.837	0.1143
Femoral neck				
g/cm^2	1.034 ± 0.534	1.057 ± 0.580	0.998 ± 0.180	0.9841
T score	0.372 ± 1.407	0.393 ± 1.427	0.275 ± 1.321	0.3726
Z score	1.169 ± 1.566	1.190 ± 1.597	1.083 ± 1.444	0.6910
Current medications for hypoparathyroidism, *n* (%)				
Calcium supplements				
Calcium carbonate (isolated formulation as tablet or powder), *n* (%)	136 (16.4)	117 (15.2)	19 (13.2)	0.2551
Dose (mg/day)	3768 ± 4356 (500–30,000)	3692 ± 3910 (500–30,000)	3400 ± 4661 (500–22,500)	0.3149
Calcium carbonate (co-formulation with cholecalciferol), *n* (%)	569 (68.6)	459 (66.9)	110 (76.4)	**< 0.0001**
Dose (mg/day)	4914 ± 3315 (1500–37,500)	4826 ± 3268 (1500–37,500)	5086 ± 2483 (1500–12,500)	0.0669
Calcium acetate (isolated formulation as tablet), *n* (%)	66 (8.0)	56 (8.2)	10 (6.9)	0.6231
Dose (mg/day)	2863 ± 1684 (700–8000)	2954 ± 1730 (700–8000)	2233 ± 1592 (700–6000)	0.3323
Total intake of elementary calcium in any form (mg/day)	1865 ± 1305 (200–15,000)	1846 ± 1355 (200–15,000)	2038 ± 1214 (200–9000)	**0.0193**
Calcitriol, *n* (%)	786 (94.7)	642 (93.6)	144 (100.0)	**0.0018**
Dose of calcitriol (mcg/day)	0.70 ± 0.38 (0.21–3.00)	0.69 ± 0.38 (0.21–3.00)	0.78 ± 0.39 (0.25–2.00)	**0.0057**
Cholecalciferol				
Cholecalciferol (in the form of drops), *n* (%)	66 (8.0)	51 (7.4)	15 (10.4)	0.2291
Dose (IU/day)	2922 ± 5676 (498–42,857)	3036 ± 6347 (498–42,857)	2479 ± 1152 (664–4500)	0.3077
Cholecalciferol (in the form of co-formulation with calcium carbonate), *n* (%)	569 (68.6)	459 (66.9)	110 (76.4)	**0.0259**
Dose (IU/day)	1656 ± 1085 (400–13,200)	1641 ± 1128 (400–13,200)	1723 ± 884 (400–4400)	0.1001
Total intake of cholecalciferol (in any form) (IU/day)	1861 ± 2173 (400–44,617)	1848 ± 2354 (400–44,617)	1913 ± 1100 (400–5180)	0.0567
Tiazide, *n* (%)	60 (7.2)	53 (7.7)	7 (4.8)	0.2275

Table 2 (continued)

	Total ($n=830$)	Surgical hypoparathyroidism ($n=686$)	Nonsurgical hypoparathyroidism ($n=144$)	p*
Hydrochlorothiazide, *n* (%)	50 (83.3)	46 (86.8)	4 (57.1)	
Indapamide, *n* (%)	10 (16.7)	7 (13.2)	3 (42.9)	
Magnesium supplements, *n* (%)	46 (5.5)	35 (5.1)	11 (7.6)	0.2264
Dose (mg/day)	376.0 ± 106.4 (104.0–730.0)	370.9 ± 105.3 (104.0–730.0)	392.3 ± 113.7 (300.0–730.0)	0.7616
rPTH (20 mcg/day), *n* (%)	2 (0.2)	2 (0.3)	0 (0.0)	
Previous History of, *n* (%)				
Renal complications				
Nephrolithiasis	66 (8.0)	57 (8.3)	9 (6.3)	0.4064
Nephrocalcinosis	6 (0.7)	5 (0.7)	1 (0.7)	0.9646
Chronic renal disease	39 (4.7)	25 (3.6)	14 (9.7)	**0.0017**
Need for renal replacement therapy	1 (0.1)	1 (0.2)	0 (0.0)	NA
Cardiac complications				
Ischemic heart disease	38 (4.6)	34 (5.0)	4 (2.8)	0.2555
Myocardial infarction	9 (1.1)	7 (1)	2 (1.4)	0.6979
Arrythmia	52 (6.3)	47 (6.9)	5 (3.5)	0.1282
CNS complications				
Cerebrovascular event	13 (1.6)	13 (1.9)	0 (0.0)	0.0959
Seizures	20 (2.4)	11 (1.6)	9 (6.3)	**0.0009**
Intracerebral calcification	34 (4.1)	17 (2.5)	17 (11.8)	**< 0.0001**
Parkinsonism	9 (1.1)	6 (0.9)	3 (2.1)	0.2029
Pyschiatric disease	67 (8.1)	50 (7.3)	17 (11.8)	0.0705
Other				
Increased frequency of infections	91 (11)	79 (11.5)	12 (8.3)	0.2664
Fracture	36 (4.3)	27 (3.9)	9 (6.3)	0.2152
Malignancy (other than thyroid carcinoma)	32 (3.9)	29 (4.2)	3 (2.1)	0.2244
Cataracts	126 (15.2)	94 (13.7)	32 (22.2)	**0.0096**

BMI body mass index, *PTH* parathyroid hormone, *sCa* serum calcium, *sP* serum phosphate, *sCre* serum creatinine, *sAlb* serum albumin, *sMg* serum magnesium, *s25(OH)D* serum 25 hydroxyvitamin D, *sALP* serum alkaline phosphatase, *BMD* bone mineral density

*Surgical versus non-surgical: p value of <0.05 was considered statistically significant

**There were 68 patients with undetectable PTH levels

DiGeorge syndrome. Previous studies reported similarly high rates of idiopathic hypoparathyroidism with low availability of genetic testing [10, 13, 18]. Despite a wider availability of testing in a Norwegian study, about one-third of nonsurgical patients remained idiopathic [12]. We believe that establishing a national registry would aid accurate classification of nonsurgical patients by facilitating access to reference centers equipped with genetic testing capabilities.

Calcitriol was the most frequently used (94.7%) medication in our cohort. Very few patients were managed with calcitriol only and most patients received one form of calcium (92.9%), predominantly as calcium carbonate in formulations combined with cholecalciferol. Previous studies reported similar rates of calcium (70–94%) and active vitamin D (84–94.7%) use, with a wide range in daily doses. Alphacalcidiol was not preferred by the physicians in our study and ergocalciferol is not available in Turkey. A significant finding in our study was the higher rates and doses for calcium and calcitriol required to treat hypocalcemia in the NSG, which might reflect a more severe disease in NSG than SG. The only other study in the literature with a similar comparison of treatment doses is the Norwegian study, where postsurgical and nonsurgical cases had similar doses for all types of treatment; however, we are unable to comment on disease severity in that study [12]. Our results showed a low rate of magnesium, thiazide and parathormone use whereas other studies reported magnesium use at approximately 20% [10] to 34% [12], thiazides at 20% [13] and recombinant parathormone at 2–17.7% [10, 12–14]. The existing studies in the literature lack the details for a head to head comparison for medication trends with our study; however, we can conclude that the treatment is highly dependent

Table 3 Demographic and laboratory characteristics of hypoparathyroidism patients according to gender

	Female ($n=674$)	Male ($n=156$)	p*
Age, years	49.4 ± 13.3	50.5 ± 14.4	0.1695
BMI, kg/m^2	29.2 ± 6.2	27.4 ± 4.4	0.0031
Duration of disease, years	9.7 ± 8.8	9.3 ± 9.8	0.0864
PTH, ng/L (15.0–65.0)	9.14 ± 7.11	6.41 ± 5.49	**< 0.0001**
sCa, mg/dL (8.5–10.5)	8.35 ± 0.96	8.33 ± 0.88	0.8471
sP, mg/dL (2.3–4.7)	4.73 ± 0.91	4.45 ± 1.00	**< 0.0001**
sCre, mg/dL (0.6–1.3)	0.78 ± 0.43	1.03 ± 0.37	**< 0.0001**
sAlb, g/dL (3.4–4.8)	4.28 ± 0.38	4.34 ± 0.41	0.0845
sMg, mg/dL (1.7–2.2)	1.74 ± 0.41	1.77 ± 0.38	0.7428
s25(OH)D, ng/mL (6.2–45.5)	25.18 ± 11.80	30.19 ± 13.76	**< 0.0001**
sALP, IU/L (40–150)	70.9 ± 41.4	69.24 ± 18.94	0.3717
BMD	n = 259	n = 49	
Lumber			
g/cm^2	1.127 ± 0.254	1.188 ± 0.237	0.1483
T score	0.417 ± 1.791	0.604 ± 1.958	0.5567
Z score	1.050 ± 1.678	0.991 ± 1.871	0.6393
Femoral neck			
g/cm^2	1.053 ± 0.569	1.010 ± 0.208	0.6594
T score	0.402 ± 1.415	0.217 ± 1.368	0.2376
Z score	1.210 ± 1.576	0.956 ± 1.512	0.3142

BMI body mass index, *PTH* parathyroid hormone, *sCa* serum calcium, *sP* serum phosphate, *sCre* serum creatinine, *sAlb* serum albumin, *sMg* serum magnesium, *s25(OH)D* serum 25 hydroxyvitamin D, *sALP* serum alkaline phosphatase, *BMD* bone mineral density

*Female versus male: p value of < 0.05 was considered statistically significant

on high doses of calcium carbonate and calcitriol and there is a lower trend for the of use of cholecalciferol, magnesium and particularly parathyroid hormone in our cohort.

In our study population, the frequency of follow-up varied, most likely reflecting physicians' recommendations regarding clinical parameters or patients' adherence to recommended examination intervals. Almost 70% of the patients in our study were followed up more frequently than every 6 months with a median calcium check of four times a year. This is a significant burden for both the patient and the health system. However, frequent calcium checks are universally required to attain stable calcium levels. In the Norway study, 82% of the patients had a sCa assessment every 6 months or more frequently [12]. According to US data, 67% of the patients had ≥ 3 and 34% had ≥ 6 calcium measurements in a year [10]. The aim of treatment is to keep sCa levels at the lower limit of the reference range or slightly below to avoid hypercalcemia and hypercalciuria [4]. The mean current albumin corrected sCa in our cohort were in the target range. However, most patients fell into the category of a normal sCa (8.5–10.5) rather than slightly below normal (8.0–8.5), which might be higher than desired for this patient group. Nevertheless, the observed rate of frank hypercalcemia was rare in our group (1.1%). Serum phosphate levels had a wider range of variation in our study but very few patients had calcium phosphate product above 55. We observed that the sCa and sP levels fluctuated over time and only one-third of the patients had a stable target range sCa over the last three measurements over one year. A remarkable finding was that NSG had a lower PTH and all time low sCa levels and a higher hypercalcemic event rate compared to the SG, which might be pointing towards a more severe disease in NSG. Our findings are supported by Mitchell et al., who reported that postsurgical patients had higher time-weighted average sCa levels than nonsurgical patients and the proportion of "calcium time-in-range" was highest in postsurgical patients compared to autoimmune and CaSR mutation patients [13]. On the other hand, a population based study from Scotland reported that the patients in the surgical group had a lower nadir PTH level than the idiopathic and nonsurgical cases [5]. The severity of disease, as roughly displayed by serum PTH of those cohorts, might serve as a predictor of wider fluctuations in sCa and sP levels. However, an important limitation that precludes PTH to be a trustable indicator of disease severity is assay variability among centers in our study as well as the effect of treatment on PTH levels.

The long-term management of hypoparathyroidism also involves the identification and management of long-term

complications. Hypercalciuria is commonly seen in chronic hypoparathyroidism patients on treatment and might cause nephrolithiasis, nephrocalcinosis and renal failure [6]. Despite close sCa follow-ups, the rate of urinary calcium measurements in our cohort was low (35.9%), similar to other epidemiological studies [12, 13]. We observed a higher rate of chronic renal disease in NSG compared to SG in our study despite a similar rate of nephrolithiasis and nephrocalcinosis. Since we were not able to identify the cause of renal failure in every patient, we cannot speculate that nonsurgical hypoparathyroidism is more frequently associated with chronic renal failure. Cranial imaging was done in almost a third of our patients and was not part of routine long-term follow-up. We noted a higher rate of intracerebral calcifications in the NSG, which might be associated with a more severe disease and more labile sCa and sP levels in this group. While the rates of parkinsonism and psychiatric disease were similar, there was a higher rate of seizures in NSG in our cohort. Vadiveloo et al. reported an increased risk of epilepsy in their study while only the nonsurgical group had increased risk of cerebrovascular disease and mental illness [11]. The Danish studies reported an increased risk of seizure, depression, neuropsychiatric diseases [19, 20]. Whether hypocalcemic episodes or cerebral white matter calcification explains the higher rate of seizures in NSG in our study remains speculative. There was an increased rate of cataracts in the NSG in our study, which contrast with findings of Vadiveloo et al. that reported an increased risk of cataracts only in the postsurgical group [11]. In a larger cohort, Underbjerg et al. found that the risk of cataracts was increased almost four times in nonsurgical group [18] while the risk was similar to the general background population for postsurgical group [20]. These studies point out that there is a nonidentical risk profile for surgical and nonsurgical groups, which might be due to higher rate of associated comorbidities and medications used in nonsurgical hypoparathyroidism patients.

Hypoparathyroidism is a state of low bone turnover that results in increased bone density [21]. Studies comparing hypoparathyroidism patients to normal population found higher DXA scores and no increase in clinical fracture risk [11, 13, 18]. However, a recent study reported higher rates of morphometric vertebral fractures detected by vertebral fracture assessment in postmenopausal women with chronic hypoparathyroidism compared to postmenopausal controls despite higher BMD values and similar trabecular bone scores [22]. We lack normal population data for such a comparison, but the DXA measurements in our study was in the higher range and the fracture rates were similar between SG and NSG.

This study provides valuable information regarding patient care in Turkey. The large sample size is the greatest strength of this study. However, there are also several limitations. Due to the registry-based retrospective nature of the study, we do not have the desired details on long-term complications of the patients. We also do not have a normal population data to compare the hypoparathyroidism associated risks. Another limitation is that these data reflect the practices of only tertiary endocrinology clinics in Turkey and not secondary and primary care. A country-wide hypoparathyroidism database with prospective patient recording is a definite need in Turkey.

In conclusion, surgery-induced hypoparathyroidism is the dominant cause of hypoparathyroidism is Turkey. There is limited availability of genetic testing in nonsurgical cases. Patients are most frequently maintained in normocalcemic range with a close follow-up by their endocrinologist. The nonsurgical patients in our cohort have a higher disease burden with a greater need for medications and increased risks of complications. We believe that this study will fuel further research needed to improve patient care in hypoparathyroidism in Turkey.

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Data Availability The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability All statistical analyses were performed using GraphPad Prism version 9.0.0 for Mac OS.

Declarations

Conflict of interest Ceyla Konca Degertekin, Dilek Gogas Yavuz, Zafer Pekkolay, Emre Saygili, Kader Ugur, Arzu Or Koca, Mustafa Unubol, Omercan Topaloglu, Berna Imge Aydogan, Nilufer Ozdemir Kutbay, Zeliha Hekimsoy, Nusret Yilmaz, Mustafa Kemal Balci, Seher Tanrikulu, Yasemin Aydogan Unsal, Canan Ersoy, Tulay Omma, Muge Keskin, Muhittin Yalcin, Ilhan Yetkin, Hikmet Soylu, Melia Karakose, Merve Yilmaz, Ersen Karakilic, Hamide Piskinpasa, Adnan Batman, Gulhan Akbaba, Gulsah Elbuken, Cigdem Tura Bahadir, Faruk Kilinc, Muhammet Cuneyt Bilginer, Ozlem Turhan Iyidir, Zeynep Canturk, Banu Aktas Yilmaz, Zeynel Abidin Sayiner, Mustafa Eroglu declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical Approval The study protocol was approved by the local ethics committee of Marmara University School of Medicine (09.2018.756). All procedures performed in this study 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.

Human and Animal Rights and Informed Consent This retrospective chart review study involving human participants was in accordance

with the ethical standarts of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standarts. The local ethics committee of Marmara University School of Medicine approved this study (09.2018.756).

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