RESEARCH

A registry for patients with chronic hypoparathyroidism in Russian adults

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Abstract

Hypoparathyroidism and pseudohypoparathyroidism are rare endocrine disorders, characterized by low serum calcium due to inappropriate parathyroid hormone (PTH) levels or resistance to its action. There is little epidemiological information regarding chronic hypoparathyroidism in Russia. This study aims to build a registry database of Russian patients with chronic hypoparathyroidism who were referred for hospital treatment in order to conduct initial analysis of clinical presentations and hospital management. The Italian registry model was taken to be able to integrate our data in the future. Two hundred patients with hypoparathyroidism ($n = 194$) and pseudohypoparathyroidism ($n = 6$) were enrolled over 2 years (2017–2019). The most frequent cause of hypoparathyroidism was neck surgery (82.5%, mostly females), followed by idiopathic hypoparathyroidism (10%), syndromic forms of genetic hypoparathyroidism (4.5%) and forms of defective PTH action (3%). Calcium supplements and alfacalcidol were prescribed in most cases. However, a minority of patients ($n = 6$) needed to receive teriparatide as the only way to maintain calcium levels and to prevent symptoms of hypocalcemia. Consequently, substitution treatment with parathyroid hormone should be available in certain cases of hypoparathyroidism. This database will be useful to estimate the potential requirement for recombinant PTH in Russia and standards for clinical and therapeutic approaches.

Key Words
- hypoparathyroidism
- teriparatide (PTH1-34)
- hypocalcemia
- parathyroid hormone.

Endocrine Connections (2020) **9**, 627–636

Introduction

Hypoparathyroidism and pseudohypoparathyroidism (PHP) are rare diseases, which are characterized by hypocalcemia due to low parathyroid hormone (PTH) or resistance to its action (1). Inadequate PTH levels result in biochemical changes: low serum calcium, hypercalciuria and hyperphosphatemia. In addition to this, inhibition of 1-α-hydroxylase causes a deficiency of 1,25 $(OH)_2$vitamin D (2). These shifts lead to an increased risk of complications (renal stones, calcifications, cardiovascular diseases, etc.) and a decline in quality of life (3). According to the recent consensus statement from the PARAT workshop, there are quite a lot of unmet needs in hypoparathyroidism (4). The estimated prevalence of chronic hypoparathyroidism ranges significantly: 5.3–58 per 100,000 in recent studies (1, 2, 3, 4, 5, 6). The most common cause is post-surgical parathyroid damage which causes chronic hypoparathyroidism when PTH is consistently inappropriately low 6 months after surgery (2, 7, 8, 9, 10). However, due to the absence of a standard definition of hypocalcemia, the incidence of

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https://doi.org/10.1530/EC-20-0219

postsurgical hypoparathyroidism varies 0–20.2% (3, 8, 9, 10, 11, 12). There are other less-frequent etiologies which may be autoimmune, genetic, infiltrative, or idiopathic hypoparathyroidism (5, 8, 13). There is still not sufficient information on the complications and quality of life in patients with different types of chronic hypoparathyroidism (4). A comparison of different treatment approaches in hypoparathyroidism on biochemical parameters or complications are not available to date. The approach to treatment varies in different countries as well (4). According to ESE guidelines, the goals of biochemical control of hypoparathyroidism are: to maintain serum calcium levels in the low to normal range; serum phosphate within the normal range and total calcium–phosphate product below 4.4 $mmol^2/L^2$ (55 mg^2/dL^2); and to avoid hypercalciuria. Treatment aims to prevent symptoms of hypocalcemia and avoid renal and extraskeletal calcifications (14, 15). In the European and Russian guidelines, calcium supplements and active forms of vitamin D3 are recommended as a standard treatment. Thiazide diuretic may additionally be given to patients with hypercalciuria (4, 14). However, side effects are commonly observed with these treatment standards such as hypercalciuria, hyperphosphatemia or extraskeletal calcifications and not all treated patients achieve their biochemical goals (4). Consequently, a minority of patients should receive recombinant human (rh)PTH1–84 as the only way to prevent symptoms of hypocalcemia (15). Recombinant PTH1–84 is approved in the USA (FDA) and in Europe (EMA) for the treatment of patients with chronic hypoparathyroidism (7). In Russia, recombinant PTH1–84 has not yet been registered, only (rh)PTH1–34 (teriparatide) is available, which is used in osteoporosis treatment.

As there is currently little epidemiological information regarding chronic hypoparathyroidism, particularly among the Russian population, we initiated an observational registry study of chronic hypoparathyroidism. This study aimed to evaluate the etiological structure, demographics, biochemical parameters, bone status, complications and hospital management of hypoparathyroidism among Russian adult referral patients.

Methods

This study adopted the design of the Italian hypoparathyroidism registry database (University of Florence) (8) in order to be able to integrate our data in the future. The Institutional Review Board of the National Medical Research Centre for Endocrinology (NMRCE) approved the study protocol.

Two hundred Russian patients were included (over 2 years 2017–2019). All data used in the database derives from the baseline evaluation reported in clinical records. We analyzed the codes corresponding to hypoparathyroidism-related diagnoses:

- Hypoparathyroidism (E20):
  a. Hypoparathyroidism (E20.0).
  b. Pseudohypoparathyroidism (E20.1).
  c. Other forms of hypoparathyroidism (E20.8) – which include autoimmune polyglandular syndrome (APS), mitochondrial disorders associated with hypoparathyroidism (including Kearns–Sayre syndrome and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes(MELAS)), DiGeorge syndrome, isolated hypoparathyroidism and hypoparathyroidism resulting from infiltrative, metastatic, ionizing damage.
- Hypoparathyroidism associated with medical intervention (E89.2).

We excluded pediatric patients (under 18 years old) and patients with the magnesium metabolism disorders (E83.4) and tetany BDU (R29.0).

The following data was analyzed: demographic data, age of disease onset, year of first assessment (baseline evaluation) at a specialized center, type of chronic hypoparathyroidism, description of type of thyroid/parathyroid surgery (in case of postsurgical hypoparathyroidism), genetic tests, clinical symptoms of hypoparathyroidism at onset and at baseline evaluation, biochemical exams of bone metabolism, instrumental exams and type of therapy at the baseline evaluation.

As in the Italian register (8), all clinical data was collected anonymously using the initials of the name and date of birth of each patient. Patients were included in the register after signing general informed consent that their data can be used for research purposes.

Statistics

Descriptive statistics are expressed as means, standard deviation of mean (S.D.) or as medians and interquartile ranges; qualitative parameters are presented as percentages with exact binomial 95% CIs. The Mann–Whitney *U*-test was utilized to compare continuous variables from two independent samples, while Fisher's exact test was used for categorical variables. Statistics were performed using

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the IBM Statistical Package for Social Sciences (SPSS20.0) for Windows (IBM).

Results

Two hundred patients were registered: 171 (85.5%) females and 29 (14.5%) males. Patients' mean age at baseline evaluation was 46 ± 13 s.d. years, 48 ± 13 s.d. years for females and 40 ± 15 s.d. years for males. Among these, six suffered from PHP: three females (50%) and three males (50%) and the mean age of these patients at baseline evaluation was lower (26 ± 7.22 s.d. years; 28 ± 8.71 s.d. years for females and 25 ± 7.02 s.d. years for males).

Etiology

Regarding etiology, the majority of cases were due to postsurgical hypoparathyroidism 82.5% ($n=165$), followed by idiopathic hypoparathyroidism 10% ($n=20$), syndromic forms of genetic hypoparathyroidism 4.5% (APS $n=7$, DiGeorge syndrome $n=1$, MELAS $n=1$), forms of defective PTH action 3% ($n=6$). There were no non-syndromic forms of genetic hypoparathyroidism or other forms of acquired hypoparathyroidism due to infiltrative diseases, copper or iron overload, or ionizing radiation exposure (Fig. 1).

Patients with postsurgical hypoparathyroidism ($n=165$) were older with a median age of 50 (42–59) compared to non-surgical hypoparathyroidism ($n=35$) with a median age of 24 (18–48) $P<0.001$. The prevalence of females in postsurgical vs non-surgical group was higher (148 (90%) females vs 23 (66%) $P=0.001$).

Type of surgery

The most frequent cause of hypoparathyroidism was neck surgery, which made middle-aged females the most common patients with hypoparathyroidism. In postsurgical hypoparathyroidism, a total thyroidectomy $n=126$ (76.4%) was the most common cause, followed by a parathyroidectomy with the removal of multiple parathyroid glands $n=23$ (13.9%), then a partial thyroidectomy $n=13$ (7.9%) followed by a parathyroidectomy with the removal of a single parathyroid gland $n=3$ (1.8%) (Fig. 2).

Pre-surgical pathologies

The most common pre-surgical pathologies were thyroid adenoma, goiter or microcarcinoma 52.8%. Thyroid cancers accounted for 31.9% of cases, sporadic primary hyperparathyroidism (s-PHPT) 11% and familial primary hyperparathyroidism (f-PHPT) 4.3% (Table 1).

Clinical presentations

The most common symptoms at disease onset were paresthesia followed by tetany. However, in 9.5% ($n=19$) of cases the patients were asymptomatic. Among the symptomatic patients ($n=181$), the prevalence of paresthesia ($n=140$) was higher than episodes of tetany ($n=102$): 77% vs 56%. The clinical findings at onset of hypoparathyroidism are shown in Fig. 3.

Upon referral to our center, 52% of patients ($n=104$) were symptomatic and 48% ($n=96$) were asymptomatic. Among the symptomatic patients, the prevalence of

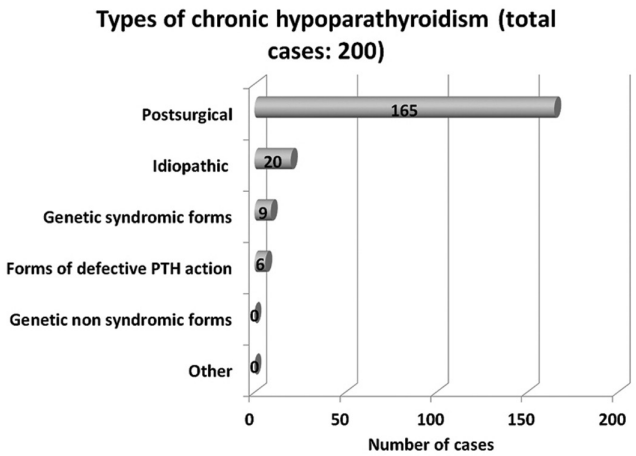

Figure 1
The prevalence of different causes of chronic hypoparathyroidism.

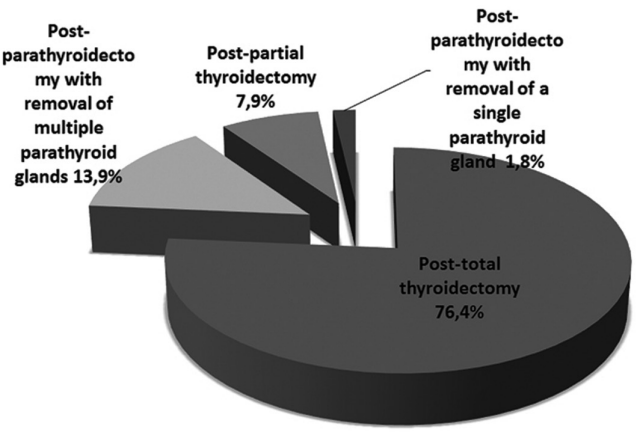

Figure 2
The types of surgical procedures, prior to the onset of postsurgical hypoparathyroidism.

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Table 1 Pre-surgical pathologies in patients with postsurgical hypoparathyroidism.

Pre-surgical pathologies	Absolute number of cases	Percentage
Thyroid adenoma/goiter/microcarcinoma	86	52.8
Thyroid cancer	52	31.9
s-PHPT	18	11
f-PHPT	7	4.3
Total	163	100
Missing data	2	-
Grand total	**165**	-

f-PHPT, familial primary hyperparathyroidism; s-PHPT, sporadic primary hyperparathyroidism

paresthesia was higher (45.2%, $n=47$); however, tetany was also commonly reported (38.5%, $n=40$). The clinical findings at baseline evaluation are shown in Fig. 4.

Dysmorphic features were presented in one case of DiGeorge syndrome, three cases of idiopathic hypoparathyroidism, one case of autoimmune polyglandular syndrome type 1(APS1), one case of MELAS and one case of PHP type1a.

Biochemical data

In patients with chronic hypoparathyroidism (total number:200), the serum levels of corrected calcium for albumin was available for 100% ($n=200$) (Table 2). Among these,only 30.5% were within the reference range (8.5–10.1 mg/dL), 17.5% were between 8.0 and 8.5 mg/dL, 67.5% were under 8.5 mg/dL, and 2% were over 10.1 mg/dL. Moreover, 100 patients (50%) had serum calcium levels under 8 mg/dL and such levels were associated with symptoms of hypocalcemia (tingling or paresthesia).

The level of serum phosphate was available for 75.5% of patients ($n=151$); among these, 53.6% ($n=81$) were within the reference range (2.5–4.9 mg/dL). Phosphate levels were under 2.5 mg/dlL in 3.3% and over 4.9 mg/dL in 43%. The levels of 24-h urinary phosphate were available for 16.5% ($n=33$); among these 66.6% ($n=22$) were within the reference range (range 13–42 mmol/24 h), under 13 mmol/24 h in 30.3% ($n=10$), and over 42 mmol/24 h in 3%. The level of serum magnesium was available for 38% ($n=76$); among these, 47.3% were within the reference range (1.8–2.4 mg/dL), under 1.8 mg/dL in 50% and over 2.4 mg/dL in 2.6%. The level of 24-h urinary calcium was available for 50% of patients ($n=100$); among these, in 40% ($n=40$) it was within the reference range (2.5–8.0 mmol/24 h), under 2.5 mmol/24 h in 39% ($n=39$) and over 8 mmol/24 h in 21% ($n=21$).

Renal function (creatinine and eGFR levels) were examined at baseline evaluation. eGFR was calculated for 153 (76.5%) patients. Overall, 34 (22.2%) had an eGFR of 60 mL/min 1.73 m^2 or below, consistent with chronic kidney disease stage 3–5.

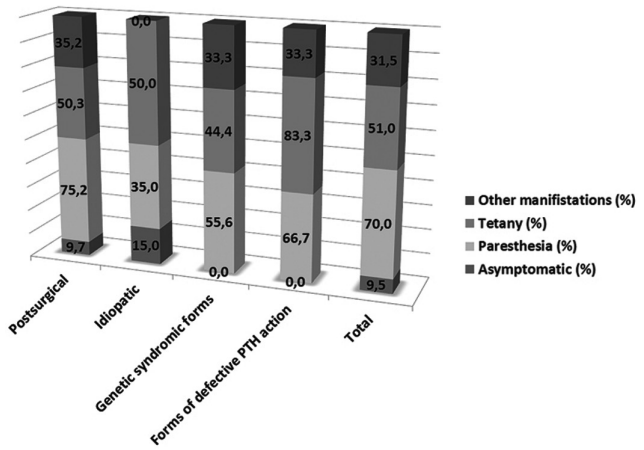

Figure 3
Clinical manifestations at onset of all presented types of hypoparathyroidism.

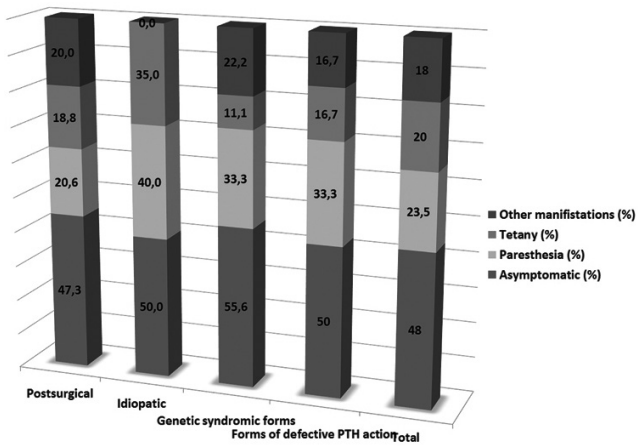

Figure 4
Clinical presentations upon referral of all main types of hypoparathyroidism.

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Table 2 Biochemical data in patients with hypoparathyroidism at the time of referral.

	Number of subjects	Percentage
The serum level of corrected calcium for albumin (mg/dL)		
Under 8.0 mg/dL	100	50
8.0–8.5 mg/dL	35	17.5
8.5–10.1 mg/dL	61	30.5
Over 10.1 mg/dL	4	2
Total	200	100
Missing data	0	
Grand total	200	
The serum level of phosphate (mg/dL)		
Under 2.5 mg/dL	5	**3.3**
2.5–4.9 mg/dL	81	**53.6**
Over 4.9 mg/dL	65	**43**
Total	151	**100**
Missing data	49	
Grand total	200	
The level of urinary phosphorus (mmol/24 h)		
Under 13 mmol/24 h	10	30.3
13–42 mmol/24 h	22	66.6
Over 42 mmol/24 h	1	3
Total	33	100
Missing data	167	
Grand total	200	
The serum level of magnesium (mg/dL)		
Under 1.8 mg/dL	38	50
1.8–2.4 mg/dL	36	47.3
Over 2.4 mg/dL	2	2.6
Total	76	100
Missing data	124	
Grand total	200	
The level of urinary calcium (mmol/24 h)		
Under 2.5 mmol/24 h	39	39
2.5–8.0 mmol/24 h	40	40
Over 8.0 mmol/24 h	21	21
Total	100	100
Missing data	100	
Grand total	200	
The level of 25OH vitamin D (ng/mL)		
Under 30 ng/mL	30	37.5
Over 30 ng/mL	50	62.5
Total	80	100
Missing data	100	
Grand total	200	

The level of 25 hydroxyvitamin D was available for 40% of the patients with chronic hypoparathyroidism ($n=80$). Among these, 62.5% were within the range of (30–100 ng/dL) and 37.5% were below 30 ng/dL.

In all patients affected by PHP (total number: 6), serum levels of calcium and phosphate were available. The levels of serum calcium were under the reference range in all cases (mean value 6.86 mg/dL ± 0.81 S.D.) and all patients had symptoms of hypocalcemia. The level of serum phosphate in all cases was over 4.9 mg/dL (mean value 5.26 mg/dL ± 0.61 S.D.). The level of PTH was increased in all cases (mean value 154 pg/mL ± 76 S.D.). Chronic kidney failure was excluded based on creatinine levels and eGFR levels (all patients had an eGFR of 95 mL/min 1.73 m^2 or higher). The level of serum magnesium was available for 20% of the patients ($n=1$), which was 1.43 mg/dL. The level of 25 hydroxyvitamin D was available for two PHP patients and was within the reference range. The level of 24-h urinary phosphate was available for 33% of patients ($n=2$), they were both within the reference range (18.1 and 21.96 mmol/24 h). In two patients with PHP, hypocalciuria ($n=2$) was recorded.

We compared the biochemical presentations of surgical and non-surgical hypoparathyroidism (idiopathic, genetic syndromic forms, pseudohypoparathyroidism). Serum calcium levels were lower and phosphate levels

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were higher in non-surgical forms of hypoparathyroidism compared to surgical hypoparathyroidism. The results of this analysis are summarized in Table 3.

Bone status

Dual-energy X-ray absorptiometry (DXA) was performed on 84 patients (42%). The median measured values were: lumbar *T* score: –0.7, *Z* score: 0.4; total femur *T* score: –0.35, *Z* score: 0.3; and femur neck *T* score –1.2, *Z* score –0.25.

In patients with chronic hypoparathyroidism, bone remodeling markers were assessed in 34% of patients ($n=68$). The mean value of bone turnover markers was low to normal.

Among non-surgical hypoparathyroidism, DXA was performed on 12 cases (34%), and Z-score was measured in all patients. The median measured values were: lumbar Z score 0.5; total femur Z score 0.3; and femur neck Z score –0.19.

Patients with surgical hypoparathyroidism were older, so *T* score was evaluated in 39 cases (24%). The median values were as following: lumbar *T* score –0.28 s.d.; total femur *T* score –0.29 s.d.; and femur neck *T* score –0.96 s.d.

The bone status of surgical and non-surgical hypoparathyroidism was not compared due to significant age difference in these groups.

Other medical data

Abdomen ultrasound tests were performed on 96 patients (48%), of whom 49 (51%) had either renal stones or nephrocalcinosis. Other radiological examinations were also performed: echocardiogram in 16% ($n=32$), X-ray examination of the skeleton in 12.5% ($n=25$), cranial CT in 11.5% ($n=23$) of total. Basal ganglia calcifications were reported in 13 cases (56%). Cardiac hypertrophy was reported in seven patients (six cases of postsurgical hypoparathyroidism and one case of Di-George syndrome). Additionally, four patients showed valvular calcifications (all cases of postsurgical hypoparathyroidism). An interventricular septal defect was identified in a patient with DiGeorge syndrome. The average duration of hypoparathyroidism before these examinations was variable (mean duration: 6 years, min: 1 year and max: 13 years).

Genetic data

Genetic analysis was done in ten subjects with a genetic diagnosis determined in six cases: one patient was diagnosed with microdeletion mutations chr. 22 (DiGeorge syndrome), three with mutations of AIRE gene (APS-1), one patient with a GNAS mutation (pseudohypoparathyroidism type 1a) and one patient with MELAS syndrome (3243A > G gene *tRNA-Leu)*.

Treatment

All patients were treated with calcium and alfacalcidol/calcitriol with a mean dose of calcium – 2.44 g/day (min: 1.25 g/day, max: 4 g/day). To be noted, 68 patients (34%) needed large amounts of calcium supplementation (> 2.5 g).

The mean dose of alfacalcidol was 1.97 mcg/day ± 1.07 mcg/day (mode: 2 mcg/day); calcitriol was taken by 15 patients, the mean dose was 0.98 mcg/day ± 0.7 mcg/day, (mode: 0.5 mcg/day); cholecalciferol was taken by 71% ($n=142$) of the total number of adult patients – 1544.71 ± 1185.78 IU/day. This conventional treatment was effective at alleviating or decreasing symptoms of hypoparathyrodism in most cases ($n=194$). However, biochemical control was totally achieved in 90 (46.4%) of cases.

In six subjects, teriparatide (rhPTH (1–34)) treatment was prescribed in addition to calcium and vitamin D. Patients were completely resistant to conventional therapy

Table 3 Comparative analysis of surgical and non-surgical hypoparathyroidism.

Parameters	**Surgical hypoparathyroidism median** (25;75 percentile) (*n* -total available cases)	**Non-surgical hypoparathyroidism median** (25;75 percentile) (*n* -total available cases)	***P*-value**
Age (years)	50 (42–59) (*n*=165)	24 (18–48) (*n*=35)	<0.001
Gender M : F	17 : 148 (*n*=165)	12 : 23 (*n*=35)	0.001
The serum levels of corrected calcium for albumin (mg/dL),	8.1 (6.9–8.8) (*n*=165)	6.7 (6.5–7.7) (*n*=35)	0.022
The serum level of phosphate (mg/dL)	4.7 (4.1–5.6) (*n*=122)	5.2 (3.9–6.4) (*n*=29)	0.046
Creatinine (μmol/L)	73 (67–89) (*n*=126)	87 (69–96) (*n*=27)	0.115

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with alfacalcidol and calcium supplementation and were available for follow-up. The mean age at evaluation was 46 ± 17 s.d. years (minimum 31 and maximum 71); the female-to-male ratio was 5:1. In four cases the subjects had postsurgical hypoparathyroidism (in three cases after thyroid surgery ($n = 2$ thyroid cancer and $n = 1$ thyroid goiter) and in one case after parathyroid surgery). Additionally, one patient had autoimmune polyglandular and one male patient suffered from idiopathic hypoparathyroidism. In three cases of postsurgical hypoparathyroidism, patients suffered from osteoporosis diagnosed before thyroid or parathyroid surgery. The longest duration of teriparatide treatment was 5 years at a dose of 20–60 mcg/day with periodically used pump therapy in a subject with APS1. Treatment with teriparatide was discontinued after achieving remission of candidiasis which led to improved gastrointestinal absorption. The other patients continued treatment with teriparatide. At the time of writing, the next longest treatment duration was 3 years at a dose of 40 mcg in a patient with gastric resection due to ulceration, followed by 2.5 years at a dose of 20 mcg per day in a female patient with colon pseudomelanosis. A male patient with severe basal ganglia calcifications due to idiopathic hypoparathyroidism received 40 mcg over 12 months and two patients had started treatment with teriparatide at a dose of 20 mcg over 6 and 7 months. The daily dose of calcium and active vitamin D were reduced and calcium levels within the reference range were achieved in all subjects. Serum phosphate was decreased in three subjects out of six. Bone mineral density (BMD) was increased in all patients with osteoporosis. Thus, severe malabsorption is the most frequent disorder requiring treatment with PTH. Teriparatide was effective in all subjects at alleviating symptoms and achieving calcium levels within the reference range.

Hydrochlorothiazide diuretic was taken by 20 patients (10%); of these, 1 was affected by idiopathic forms and 19 by postsurgical forms of hypoparathyroidism.

In patients affected by PHP, the mean doses of calcium and alfacalcidol supplementation were, respectively, 2.6 ± 1.29 g/day and 2.4 ± 0.54 mcg/day; cholecalciferol was additionally taken in three cases (1066 ± 832 UI/day). Two patients needed large amounts of calcium supplementation (> 2.5 g).

Discussion

This is the first report of clinical presentations and treatment approaches in Russian patients with hypoparathyroidism referred to specialized care. The analysis has shown that the most frequent cause of hypoparathyroidism was neck surgery, which made middle-aged females the most common patients with hypoparathyroidism, as described in literature (3, 5, 7, 8, 10, 11). Postsurgical hypoparathyroidism occurred after a total thyroidectomy in most cases, following by a parathyroidectomy and then a partial thyroidectomy. The most common pre-surgical pathologies were thyroid adenoma, goiter or microcarcinoma which is similar to other countries' data (18). Thus, the demographic and etiological structure of the hypoparathyroidism in Russian adults is consistent with the results of other registries including the Italian database (8). Data relating to non-surgical forms of hypoparathyroidism is not yet well defined. In Denmark according to the national register, 180 patients with non-surgical hypoparathyroidism were estimated, the prevalence being 2.3/100,000 (18). In Italy and Norway, the most common non-surgical forms were patients with defective PTH action and the prevalence was 1.3/100,000 (5, 8). According to our data on non-surgical forms, the majority of cases were classified as idiopathic hypoparathyroidism (10% of total). In a few cases we identified known genetic causes (4.5%) and forms of defective PTH action (3%). The diagnosis of PHP was based on clinical characteristics and endocrine findings, also in one case it was confirmed through molecular genetic testing. We directly compared the clinical and biochemical presentations of surgical and non-surgical hypoparathyroidism among our referral population. As expected, patients with post-surgical hypoparathyroidism were older. The majority of cases in both surgical and non-surgical hypoparathyroidism were females, but there were statistically significantly more females with surgical hypoparathyroidism. Upon referral, patients with non-surgical hypoparathyroidism had lower calcium and higher phosphate serum levels, which shows a more severe clinical presentation in non-surgical hypoparathyroidism.

Common complications of hypoparathyroidism are hypercalciuria and hyperphosphatemia due to low calcium reabsorption in the kidneys, treatment with calcium supplements and a lack of the inhibitory effect of PTH on phosphate reabsorption in the kidneys. All of these biochemical abnormalities were present in up to 40% of our patients indicating poor compensation. Moreover these biochemical tests were not registered in the medical records of almost 50% of patients which may require additional attention. The next most prevalent complications are renal abnormalities. Renal function (creatinine and eGFR levels) was calculated for

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76.5% ($n=151$) of patients. Among them, 22.2% ($n=34$) had an eGFR of 60 mL/min 1.73 m^2 or below, consistent with chronic kidney disease stage 3–5. In a study by Mitchell *et al*. (19), eGFR was calculated for 107 patients and chronic kidney disease stage 3 or higher was identified in 41% of cases, which is more prevalent than in our study. Perhaps the duration of observation in the study of Miller *et al*. was longer. Abdomen ultrasound tests were performed on 96 patients (48%), of whom 49 (51%) had either renal stones or nephrocalcinosis. In the study by Mitchell *et al*. (19), 54 patients were examined using ultrasound, of whom 17 (31%) had signs of nephrolithiasis. It was found that the rates of chronic kidney disease stage 3 or higher are between 2 and 17 times more prevalent in hypoparathyroidism patients compared to an age matched control group (19).

It is known that a deficiency of vitamin D and magnesium can lead to hypocalcemia (24). Therefore, it is important to provide adequate supplementation of cholecalciferol and magnesium in patients with hypoparathyroidism. However, not all patients with hypoparathyroidism had data available with regards to magnesium and vitamin D levels. In cases where this data were available, magnesium deficiency was confirmed in 50% of cases (magnesium levels below the reference range) and vitamin D deficiency in 37.5% of all cases (serum 25 hydroxyvitamin D concentration was under 30 ng/dL). Hypoparathyroidism is characterized by low bone metabolism, explaining why bone mineral density (BMD) is usually normal or higher than normal, except after a parathyroidectomy for PHPT (8, 12, 23, 24). A DXA exam was carried out at baseline evaluation for half of the patients and showed normal to high values and a low bone turnover profile typical of the disease. Regarding cardiovascular complications which are common in hypoparathyroidism due to ectopic calcification, only 32 patients underwent cardiovascular evaluation. Another very common complication is ectopic calcifications in the brain (8, 13, 23, 25). Among patients who underwent CT, in 13 cases (56%) basal ganglian calcifications were found.

Regarding clinical symptoms at baseline evaluation, around half of the patients (52%) were symptomatic, which is similar to the Italian data (8). Accordingly, symptomatic patients had a greater prevalence of paresthesia (36%) than epizodes of tetany (17%) (8). Similarly, in the presented study, among the symptomatic patients, the prevalence of paresthesia was higher 45.2% ($n=47$) than episodes of tetany 38.6%($n=40$) .

The management of chronic hypoparathyroidism is problematic (13, 14, 16, 17, 19, 20, 21, 22) and varies in different countries (4). In a Danish study, alfacalcidol was exclusively used (1, 7), whereas calcitriol is mostly prescribed in the USA (19). The use of supplemental calcium differs as well, being highest in the USA, whereas higher doses of active vitamin D are used in Europe (4). From our study, standard treatment in Russia appears to be oral calcium supplements and alfacalcidol, which were sufficient at alleviating or minimizing symptoms in almost all patients (97%) and maintaining calcium and phosphate levels in almost half of cases. Among our referral population, 34% required large amounts of calcium and vitamin D supplementation, which is often associated with severe, long-term future complications such as nephrocalcinosis, cataracts and basal ganglia calcifications.

In addition to this, it was necessary for some patients to receive teriparatide as the only way to maintain calcium levels and to prevent symptoms of hypocalcemia. It seems that malabsorption due to gastrointestinal disease was the most common disorder requiring PTH replacement. The need for PTH replacement is likely more extensive, as only 48% achieved all therapeutic goals on conventional treatment in a short-term observation. However, in Russia, teriparatide is available only for osteoporosis treatment, so it was not prescribed in all required cases. Consequently, substitution treatment with parathyroid hormone should be available in certain cases of hypoparathyroidism (26).

Our study has several limitations. This research implies all the limitations related to the observational design of a registry study and consequent absence of some clinical data as is frequently the case in real clinical practice analysis. Another limitation was that patients with mild presentations of hypoparathyroidism may have been underestimated because of the referral population. In addition to this, the study is a first attempt to build a hypoparathyroidism registry in a single center and, therefore, this data does not fully represent the epidemiology of chronic hypoparathyroidism, the exact prevalence and the potential need for recombinant PTH in Russia. We also excluded pediatric patients because the study was conducted in adult departments.

In conclusion, this is a first analysis of patients referred for hospital management with hypoparathyroidism. It reveals the clinical presentations of insufficiently controlled patients, certain underestimations of potential complications according to the prevalence of performed

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tests and a lack of standardized approaches to the assessment of patients with hypoparathyroidism. A small proportion of patients received rhPTH 1–34 in order to control hypocalcemia. However, the long-term benefit of this treatment is unknown and calls for additional examination.

Declaration of interest
The authors declare that they have no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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

Acknowledgements
The authors thank Geoffrey Clayson for English editing work.

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Received in final form 15 May 2020
Accepted 4 June 2020
Accepted Manuscript published online 4 June 2020