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ORIGINAL ARTICLE

BIOCHEMICAL CONTROL OF 78 PATIENTS WITH CHRONIC HYPOPARATHYROIDISM REFERRED BETWEEN 2006 AND 2020 – WHERE DO WE ACTUALLY STAND?

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Abstract. *Hypoparathyroidism (hypoPT) is a relatively rare endocrine disease, mainly due to thyroid surgery. The classical supplementation with calcium and active vitamin D may represent a challenge to the clinician.* ***Objective:*** *To describe the level of biochemical control in patients with chronic hypoPT and to look for differences between postsurgical and non-surgical cases referred between 2006 and 2020.* ***Materials and Methods:*** *This was a retrospective cross-sectional study with data review from the database of a tertiary endocrine clinic from the last 15 years. Cases with hypocalcemia not related to PTH were excluded. The patients' medical history was reviewed as well as concomitant diseases and medications. Serum calcium (total, albumin-corrected and ionized; sCa, corrCa, iCa^{+}) and phosphates (P), magnesium, creatinine, alkaline phosphatase together with 24hr urinary calcium and phosphate were measured. The intact parathyroid hormone (iPTH) was determined by electro-hemi-luminescence (Elecsys, Roche Diagnostics). Thyroid and abdominal ultrasound (US) were both performed.* ***Results:*** *Seventy-eight patients met the study criteria – 69 were females. Most of them were between 30 and 60 years (mean age 50.6 ± 14.5 years). Albumin-corrected calcium was in target in 20.5% of the patients, ionized calcium – in 36.5%, serum phosphate – in 46.3%, serum magnesium – in 87.9%. When all four parameters were taken together, less than 20% were in target. Hypercalciuria was registered in 11.8%, while 57.1% of the patients had nephrolithiasis and 27.3% had CKD grade 3-4. Thus, a high proportion of patients with kidney involvement was identified. Calcium carbonate and calcitriol were the preferred replacement choices. Comparing patients with post-surgical and non-surgical hypoPT significant differences were found only for age, total serum calcium, serum magnesium and TSH.* ***Conclusion:*** *Our study is the first of its kind in our country during the last two decades describing the contemporary clinical and biochemical picture of chronic hypoPT in patients referred for specialized care. Low supplementation doses leading to hypocalcemia and hyperphosphatemia were a common finding. Low patient's adherence may be just one possible explanation. Non-surgical cases tend to have even lower calcium and magnesium levels. The patients, their families and treating physicians should be better informed about up-to-date management of chronic hypoPT and the possible impact of suboptimal treatment on morbidity and mortality of the affected subjects.*

Key words: *parathyroid glands, chronic hypoparathyroidism, laboratory findings, comorbidities*

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INTRODUCTION

Hypoparathyroidism (hypoPT) is a relatively rare endocrine disorder characterized by inappropriately low secretion of parathyroid hormone (PTH) with resulting low calcemia [1, 2]. In the last two decades its most common etiology is iatrogenic injury to the parathyroid glands during thyroid surgery, which accounts for more than 75% of all cases of chronic hypoPT [3, 4]. However, idiopathic and autoimmune forms of hypoPT can still be diagnosed in clinical practice. Chronic hypoPT after thyroid/parathyroid surgery is diagnosed if hypocalcemia / low PTH levels persist for longer than 6 months [3, 5-7]. Postoperative hypoPT might be expected in 6-12% of all thyroidectomies [7, 8]. Risk factors for the development of postsurgical hypoPT are big-size goiters, Graves' disease and extensive neck explorations due to malignant disease.

The replacement treatment for hypoPT is lifelong and consists of calcium supplements and active vitamin D metabolites [3, 5-7, 9, 10]. More recently, recombinant human PTH (rhPTH) has been introduced in the USA and several other countries for the treatment of resistant cases requiring very high doses of traditional calcium / vitamin D replacement [11, 12]. The goal of treatment is to maintain albumin-corrected serum calcium in the lower reference range (2.1-2.3 mmol/l) together with normal serum phosphates and magnesium [5, 7].

The treatment success is tightly bound to the patients' compliance. A few medications can alter the absorption of calcium salts (like proton-pump inhibitors, PPI). Biochemical follow-up is very important for proper adjustment of calcium/vitamin D doses [7].

The **aim of the present study** was to describe the level of biochemical control in patients with chronic hypoPT and to look for differences between postsurgical and non-surgical cases.

MATERIALS AND METHODS

Design

This was a retrospective observational cross-sectional study based on hospital chart review of routine clinical care in our tertiary endocrine clinic. All patients had given their informed consent for hospitalization and their data handling. All procedures 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. The inpatients' hospital records for the last fifteen years were searched through with the keyword "chronic hypoparathyroidism".

One-hundred and two positive patient records were identified between 2006 and 2020. Chronic hypoPT was defined as a combination of low albumin-corrected or ionized serum calcium and inappropriately low parathyroid hormone (PTH) before supplementation with calcium/active vitamin D [1, 2]. Postsurgical hypoPT was confirmed if the above changes had persisted for at least 6 months after thyroid/parathyroid surgery [3]. Other causes for hypocalcemia were excluded including but not limited to: CKD grade 5, malabsorption syndromes, hypercalciuria due to other causes (loop diuretics, idiopathic, etc.), pseudohyperparathyroidism [4, 13]. Ten cases had incomplete data and were not included in the analyses. Seventy-eight patients had complete records and were included. The primary reason for their referral to the clinic had been the need for biochemical follow-up and for proper adjustment of the patients' calcium/vitamin D supplementation.

Laboratory and hormonal data

Total serum calcium had been measured by a photometric assay (reference range 2.12-2.62 mmol/l) and whenever possible by atomic absorptiometry – Ca-AAS. Albumin-corrected calcium was calculated based on a mean albumin of 44 g/l (local lab reference range for albumin 35-52 g/l; and for corrected sCa 2.10-2.60 mmol/l). Ionized calcium (iCa+) had been measured by atomic absorptiometry (reference range 1.1-1.3 mmol/l). Data on serum magnesium (reference range 0.65-1.10 mmol/l) and phosphates (0.81-1.45 mmol/l) were also present.

Intact PTH (iPTH) had been measured by a second generation assay (Elecsys, Roche Diagnostics, Switzerland) and expressed in pmol/l (reference range 1.59-6.89 pmol/l).

Serum creatinine had been measured by a colorimetric method and the estimated glomerular filtration rate (eGFR) calculated according to the MDRD-formula in ml/min/1.73 m². Urinary excretion of calcium and phosphate were measured from 24h urinary samples in mmol/24 hr (reference ranges 2.5-8.0 mmol for calciuria and 13-42 mmol for phosphaturia).

Imaging

The imaging included neck ultrasound of all patients (using a linear 9-12 MHz transducer, including Doppler imaging). In cases of a visible thyroid parenchyma its volume was calculated by multiplying the three diameters (anterior-posterior, medial-lateral, proximal-distal) and dividing the product by a factor of 0.48 (formula for ellipsoids).

Statistical analysis

All analyses were performed with the SPSS 13.0 for Windows platform (SPSS Corp., Chicago, IL). Descriptive statistics and frequency analysis were performed. Missing data were not replaced. Most of the data were positively skewed, thus medians and quartile ranges were preferred. The Mann-Whitney and Wilcoxon tests were used for comparisons of independent and dependent samples. Statistical significance was set at $p < 0.05$.

Results

Among the 102 screened patient records with the diagnosis of hypoparathyroidism, 78 patients met the definition of chronic hypoPT and their records contained sufficient data for analysis (69 females and 9 males). Their mean age was 50.6 ± 14.5 years (range 23 – 81 years). Their distribution according to age was as follows: 21-30 yrs – 5.1%; 31-40 yrs – 25.7%; 41-50 yrs – 20.5%; 51-60 yrs – 23.1%; 61-70 years – 12.8% and > 70 yrs – 12.8% (see also Fig. 1).

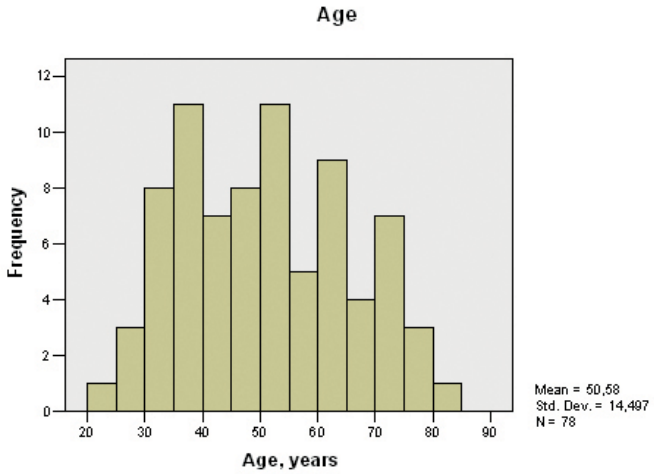


Fig 1. Age distribution of the 78 included patients with chronic hypoPT

The etiology of the hypoPT was post-surgical due to thyroidectomy in 60 cases (76.9%) and due to parathyroidectomy – in 3 cases (3.8%). The remaining 15 cases (19.2%) were classified as non-surgical (possibly idiopathic) hypoPT. The mean duration of the hypoPT was 9.8 years (± 12.2 yrs) with a median of 5.5 years. It was less than 1 year in 35.9%; between 1 and 5 years – in 14.1%; between 5 and 10 years – in 15.4%; ≥ 10 years – in 34.6%.

The biochemical and hormonal data of the patients on their first day in hospital are presented in Table 1. The frequency distribution of normal/abnormal laboratory values is displayed in Table 2. Albumin-corrected calcium was ≥ 2.10 mmol/l in 30.3% only and in the target range of 2.10-2.30 mmol/l in 26.5% only. None of the patients presented with hypercalcemia (> 2.60 mmol/l). 84.1% of the patients had values of ionized calcium below the lower limit of the

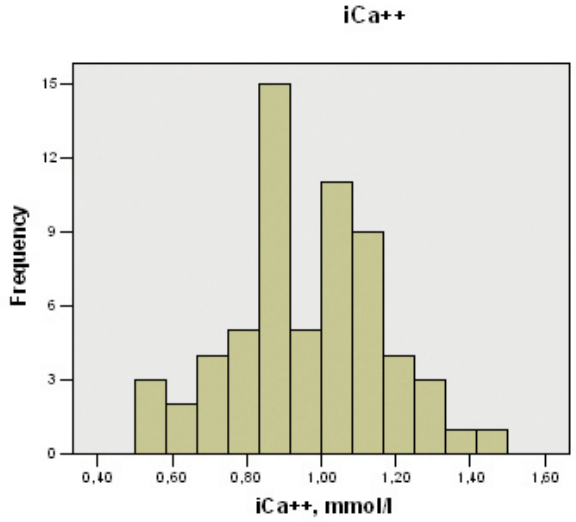
Table 1. The biochemical and hormonal data of the patients with hypoPT during their hospital stay for biochemical follow-up and therapy adjustment are presented as means ± SD and medians with quartiles

		sCa mmol/l	iCa++ mmol/l	sP mmol/l	sMg mmol/l	Creatinine µmol/l	Albumi ng/l	Ca X P, mmol²/l²	PTH pmol/l	eGFR ml/min/m²	uCa mmol/24 hr	Phosphate mmol/24 hr	Calcium daily mg	Levothyroxine µg	TSH UI/L
N with data		77	63	77	66	76	74	67	73	75	68	68	60	52	66
Mean		1.92	0.96	1.50	0.71	86.9	40.5	2.90	1.03	69.1	4.33	14.25	1417.8	100.3	7.32
Std. Dev.		0.32	0.20	0.27	0.08	27.2	5.0	0.61	1.03	21.8	6.67	14.15	547.7	42.7	15.70
Median		1.96	0.98	1.44	0.72	83.0	41.0	2.86	0.80	66.7	2.69	11.68	1200.0	100.0	2.54
Minimum		1.19	0.54	1.05	0.45	47.0	25.0	1.74	0.10	19.6	0.22	0.10	180.0	25.0	0.00
Percentile	25	1.68	0.85	1.30	0.68	69.0	37.0	2.47	0.41	55.4	1.15	7.63	1200.0	63.8	1.07
	75	2.20	1.13	1.69	0.76	97.8	44.0	3.39	1.39	82.4	4.67	17.56	1800.0	125.0	4.72
Maximum		2.58	1.45	2.30	0.85	218.0	49.0	4.76	6.24	145.0	48.30	100.00	3000.0	200.0	100.0

local lab of 1.16 mmol/l with 2 patients (3.2%) having values ≥ 1.32 mmol/l (upper normal limit of local lab). The distribution of ionized calcium levels and serum phosphates is shown in Fig. 2. Serum phosphates were elevated in more than half of the study sample with 5 patients (6.4%) showing alarming values ≥ 2.0 mmol/l. The calcium phosphate product exceeded 4.4 $mmol^2/l^2$ in only 1 patient out of 78.

Table 2. The frequency distribution in percentages of normal/abnormal (in target/outside target) laboratory values is displayed

Laboratory parameter	Frequency, %	Local lab range
Albumin-corrected calcium, mmol/l		2.10-2.60
≤ 1.9 mmol/l	47.1%	mmol/l
1.90-2.09 mmol/l	22.6%	
2.10-2.29 mmol/l	20.5%	
2.30-2.59 mmol/l	9.8%	
Ionized calcium, mmol/l		1.16-1.32
< 1.0 mmol/l	54.0%	mmol/l
1.10-1.20 mmol/l	36.5%	
> 1.20 mmol/l	9.5%	
Serum phosphates, mmol/l		0.81-1.45
In normal range (≤ 1.45 mmol/l)	46.3%	mmol/l
Mildly elevated (>1.45 – ≤ 1.70 mmol/l)	30.9%	
Severely elevated (> 1.70 mmol/l)	22.8%	
Serum magnesium		0.65-1.10
< 0.65 mmol/l	12.1%	mmol/l
In range	87.9%	
iPTH, pmol/l		1.20-6.90
< 1.20 (below normal range)	83.6%	pmol/l
≤ 2.30 (low normal)	13.7%	
> 2.30 (in range)	2.7%	
Urinary calcium, mmol/24 hr		♀: 2.50-6.50
< 2.50 mmol/24 hr	45.6%	mmol/l
In range	32.6%	♂: 2.50-7.00
> UNL (6.50 ♀; 7.00 mmol/l ♂)	11.8%	mmol/l
Urinary phosphate, mmol/24 hr		13.0-42.0
< 13.0 mmol/l	55.9%	mmol/24hr
In range	41.1%	
> UNL	3.0%	
eGFR, ml/min/1.7 m^2 (MDRD-formula)		
15-29 (CKD grade 4)	2.7%	
30-59 (CKD grade 3)	24.6%	
60-89 (CKD grade 2)	56.7%	
90-119 (CKD grade 1)	13.3%	
≥ 120	2.7%	
TSH, UI/L	66 patients	0.3-4.2 UI/L
< 0.3 UI/L	10.6%	
In range	56.1%	
4.2-10 UI/L (subclinical hypothyroidism)	21.2%	
> 10 UI/L (overt hypothyroidism)	11.1%	



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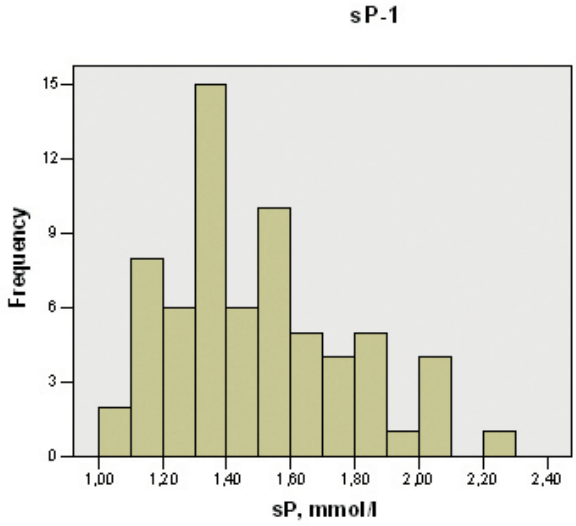

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Fig. 2. Frequency distribution in mmol/l of: **A**) ionized calcium; and **B**) serum phosphates

Data on TSH were available from all 66 patients with post-surgical hypoPT. A total of 33.3% showed values above the ULN (> 4.2 mIU/l) indicating possible insufficient thyroid hormone replacement.

Imaging data

Data from renal ultrasound were available in 68 patients (80.8%). Kidney stones were diagnosed in 57.1% of them with 9.5% having microcalculi (≤ 4.0 mm), 42.9% – calculi > 4.0 and ≤ 8.0 mm; and 4.8% – bilateral nephrolithiasis.

All patients with post-surgical hypoPT had thyroid remnants visible on US – their volumes ranging from 1.1 ml to 19.6 ml. Solitary thyroid nodules were seen in 3 cases (3.8%) and multiple nodules – in 4 ones (5.1%).

Calcium/vitamin D replacement

All participants received vitamin D supplementation with nine of them (11.5%) taking cholecalciferol only. The preferred active metabolite was calcitriol (62 pa-

tients – 79.5%), while the remaining seven patients on active metabolites (9.0%) were receiving calcidiol (alfacalcidiol). The majority were taking 0.5 and 0.75 mcg calcitriol daily – 28.6% and 34.9% of the whole sample, followed by 1.0 mcg daily – 11.1%. Three patients only were taking > 1.0 mcg and ≤ 2.0 mcg daily with 2.0 mcg being the highest dose prescribed.

Calcium carbonate was the preferred calcium supplement (69 pts – 88.5%). The mean daily dose was 1417 mg, while the median -1200 mg. Eight patients (10.3%) were taking ≤ 600 mg elementary calcium daily, while twenty-five (32%) were taking 1200 mg and another twenty (25.6%) – 1800 mg daily. The highest daily dose was 3.0 grams (1 patient).

Recombinant PTH is not registered in our country and no data on its use could be found in our sample.

Fifty-two patients (82.5% of all post-thyroidectomy patients) were taking levothyroxine. The mean and median of the daily dose were equal – 100 mcg. The distribution of the daily calcium supplementation and levothyroxine dose is displayed in Fig. 3.

Concomitant diseases

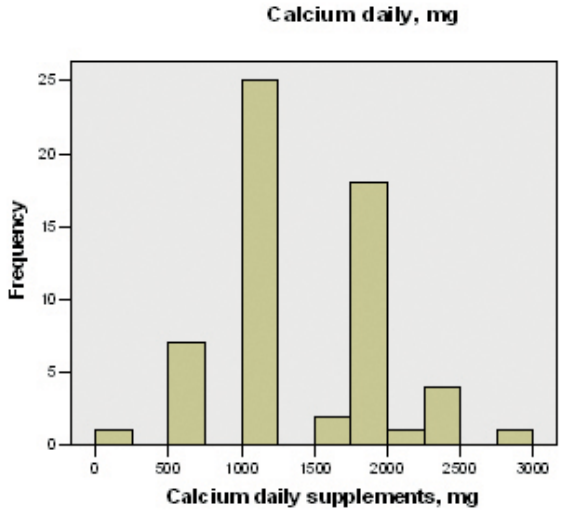
Data on thyroid autoimmunity were available from 55 patients (70.5% of the whole sample). Seventeen patients had been operated due to Graves' disease (21.8%), while 6 had autoimmune thyroiditis (7.7%).

The most frequently reported co-morbidity was arterial hypertension – 44 participants (56.4%), which was an isolated abnormality in 20 of them (45.5% of the hypertensive subgroup). Eleven patients (14.1%) had coronary artery disease with 5 of them having survived myocardial infarction. Two patients (2.6%) reported heart failure and another two (2.6%) – history of stroke.

Malignancy as the cause for the previously performed thyroidectomy was identified in 15 patients (22.0% of the thyroid postsurgical group): papillary thyroid carcinoma (PTC) in 12 patients (15.4% of the thyroid postsurgical group), follicular thyroid carcinoma (FTC), sarcoma and thymoma – 3 patients in total, each one in 1 patient (6.7% of the postsurgical group). One patient had been operated for lymphoma of the thyroid. Radioiodine ablation had been reported by 7 patients.

Surgical versus non-surgical hypoPT

Comparing patients with post-surgical and non-surgical (idiopathic) hypoPT, significant differences were found only for age, as well as for levels of total serum calcium, serum magnesium and TSH (see Table 3).



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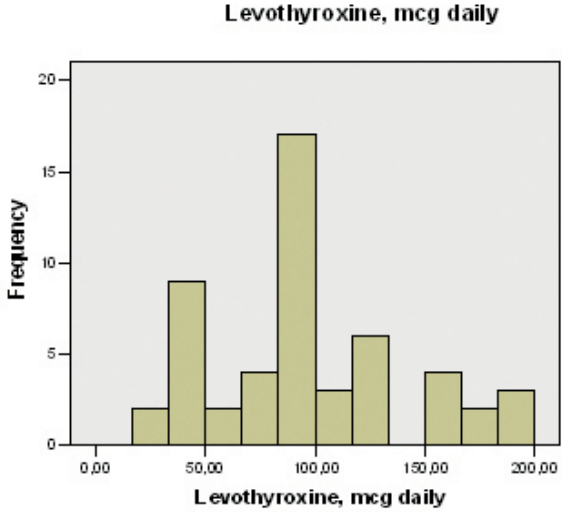

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Fig. 3. Distribution of the daily calcium carbonate dose (**A**) and the levothyroxine dose (**B**) in the study sample

Table 3. Significantly different parameters between the surgical and non-surgical subgroups of hypoPT

Significantly different parameters	Type of hypoPT	Mean	Standard Deviation	Std. Error Mean	Significance, p
Age, years	Post-surgical	52.5	14.0	1.8	0.023 a
	Non-surgical	43.0	14.7	3.8	
Total sCa, mmol/l	Post-surgical	1.99	0.28	0.04	0.030 b
	Non-surgical	1.67	0.36	0.10	
Serum Mg, mmol/l	Post-surgical	0.73	0.06	0.01	0.034 a
	Non-surgical	0.68	0.086	0.024	
TSH, UI/L	Post-surgical	8.57	17.12	2.33	0.006 b
	Non-surgical	1.79	1.42	0.47	

a – equal variances assumed, b – equal variances not assumed.

The non-surgical patients with hypoPT were of younger age and had significantly lower levels of serum calcium, magnesium and TSH.

DISCUSSION

We did a retrospective hospital chart review of patients with chronic hypoPT referred for regular follow-up to our tertiary endocrine clinic in the time period 2006-2020. We registered a very low proportion of patients with normal calcium-phosphate metabolism: albumin-corrected calcium was in target in 20.5%, ionized calcium – in 36.5%, serum phosphate – in 46.3%, magnesium – in 87.9%. If all four parameters taken together, less than 20% were in target. More than half of the patients (57.1%) had nephrolithiasis and 27.3% had CKD grade 3-4 indicating a surprisingly high proportion of patients with kidney involvement. Calcium carbonate and calcitriol were the preferred replacement drugs. Our study indicated insufficient calcium/vitamin D supplementation warranting thorough data review and evolving management strategies for better adherence and quality of life.

We compared our results on reaching targets of calcium/vitamin D supplementation with already published data from other cohorts of patients with chronic hypoPT (see Table 4). Table 4 shows that serum levels of total (albumin-corrected) calcium and phosphates in our sample were less well corrected than in the studies under comparison. On the contrary, data on serum magnesium, urinary calcium and glomerular filtration did not differ substantially.

Considering the insufficient biochemical control of hypoPT in our study population a number of reasons might be listed. First, all patients were hospitalized ones, thus introducing a bias toward more severe and uncontrolled disease. Second, for the study period active vitamin D metabolites were reimbursed in our country while calcium salts were prescribed out-of-pocket. This predisposes patients' adherence to vitamin D metabolites only. And third, one should not underestimate the patients' concerns about side effects. In the case of calcium salts these include gastrointestinal complaints (e.g. obstipation, flatulence and others), risk for vascular calcifications and renal stones [17-19]. Different strategies have been implemented by other authors to overcome these worries – alternate calcium intake or even "no calcium" regimens [20, 21]. The most common worries about calcitriol are kidney damage and polyuria as already reported in a different study with 64 patients [20]. Calcitriol has actually been linked to declining renal function and risk for polyuria and nephrolithiasis [22-25]. Coming back to poor biochemical control of our patients, one must keep in mind that it is clearly linked to a higher risk for complications and worse quality of life as reported elsewhere [25-27].

The supplementation doses reported by the patients in our study might also be a bit lower than the optimal ones [3, 5]. Forty-two percent of the subjects on calcium carbonate were taking ≤ 1200 mg daily while 63.5% of those on calcitriol were taking daily doses in the range 0.5/0.75 μg which might not always be sufficient as indicated in up-to-date clinical guidelines on hypoPT [3, 5, 6]. The suboptimal dosage might be due to both clinicians' and patients' preferences and, of course, to financial reasons. Another preliminary study revealed that one-third of the patients may lack motivation to use calcium whereas half of all may be anxious about possible side effects [19]. In this particular study one third of the patients were taking oral calcium and calcitriol less than the recommended dose [18]. A UK national chronic hypoPT audit identified 80 individual patients' cases and reported compliance with treatment standards between 98.8% and 60%, whereas the compliance with monitoring standards fell even lower – 91.3-20% [28]. In a German survey on management of hypoPT by family physicians only 75.8% of the patients had data on serum calcium and one third of them still showed hypocalcemia [29].

Table 4. Data on reaching targets of calcium/vitamin D supplementation – comparison with already published observations

Parameter under study*	Our data	Russian Registry [14]	Canadian Registry [15]	Turkish study [16]
Number of subjects	78	544	130	107
Hypocalcemia	69.7%	44.2%	58%	68.1%
High phosphates	53.7%	63.1%	29%	46.2%
Low magnesium	12.1%	23.6%	12%	
Hypercalciuria	11.8%	37.6%	36%	43.7%
eGFR < 60 ml/min/1.73 m^2	27.3%	15.8%	23%	

* According to specific lab reference values applied in the studies

Concerning possible differences between surgical and non-surgical cases we confirmed the tendency for non-surgical patients to be younger and to present with deeper hypocalcemia and hypomagnesiemia. This finding has already been reported in previous studies by other authors [14, 30]. The reasons behind these differences are not yet clearly elucidated but surely refer to the different etiology of hypoPT (lack of parathyroid tissue versus autoimmune or invasive destruction of the parathyroid cells and secretion) [31]. As expected TSH was normal in our non-surgical cases while it was suboptimal in a great number of post-surgery participants meaning that poor adherence to levothyroxine treatment might parallel that to the calcium/vitamin D replacement.

We were struck by the high prevalence of nephrolithiasis in our patients studied with renal ultrasound – 57.1%. At the same time hypercalciuria was relatively uncommon (in 11.8%). In other detailed studies the prevalence of renal stones had been reported as low as 32.5% [14] or even < 27% [15]. The detrimental impact of the hypoPT itself on the kidney has already been documented [23]. However, our results on such a high rate of renal stones warrants further analysis and follow-up.

Our study has some limitations. First, we included patients referred to a specialized endocrine center introducing a bias towards more difficult to control cases. Second, the presented data are cross-sectional ones and longitudinal follow-up might have added further value. Third, the number of patients was rather modest therefore not allowing detailed sub-analyses.

CONCLUSION

The major strength of our study was that it described the contemporary clinical and biochemical picture of chronic hypoPT in patients referred for specialized care. Low supplementation doses leading to hypocalcemia and hyperphosphatemia were a common finding. Low patient's adherence may be just one possible explanation. The non-surgical hypoparathyroid patients were of younger age and had significantly lower levels of serum calcium and magnesium. All the hypoparathyroid patients, their families and treating physicians should be better informed about up-to-date guidelines on hypoPT [32] and the possible impact of suboptimal treatment on morbidity and mortality in hypoparathyroid subjects [33, 34]. Unfortunately, we do not know with certainty yet, whether the introduction of treatment of hypoPT with rhPTH might be of substantial benefit to our not well-controlled patients [35].

Ethical considerations

All patients had given their informed consent for hospitalization and data handling.

Disclosure Summary: *The authors have nothing to disclose.*

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