HIPOPARA-RED, REAL LIFE EXPERIENCE IN 322 PATIENTS WITH HYPOPARATHYROIDISM

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Abstract

***Context*:** Hypoparathyroidism is a rare disease and as such, its natural history, long term complications and correct clinical management remain unclear.

Objective: To describe the natural history and clinical characteristics of the disease.

Design and setting: Topresent a retrospective observational analysis from seven specialized centers in Buenos Aires, Argentina.

Patients: chronic hypoparathyroid patients followed up between 1985 and December 2018.

Main Outcome Measures: data on demographics, etiology, clinical complications, biochemical parameters, DXA values and treatment doses were collected.

Results: 322 subjects with chronic hypoparathyroidism were included, 85.7 % were female. Mean age was 55.2 ± 16.8 years and mean age at diagnosis was 43.8 ± 16.8. Prevalence of surgical hypoparathyroidism was 90.7 %, most common causes being thyroid carcinoma and benign thyroid disease. A history of hypocalcemia requiring hospitalization was present in 25.7 % and 4.3 % had a history of seizures. Overall, 40.9 % had reported at least one neuromuscular symptom. Renal insufficiency was present in 22.4 % and was significantly associated with age ($p<0.0001$). Hyperphosphatemia was present in 42 %. A history of severe hypocalcemia, paresthesias, tetany, ganglia calcifications, seizures and cataracts was significantly higher in nonsurgical patients. ***Conclusion****:* Although these patients were followed up by experienced physicians, clinical management was heterogeneous and probably insufficient to assess all the potential complications of this chronic disease. Almost 70 % of this group of patients met the experts´ indications for considering the use of rhPTH 1-84. Being aware of this fact is the first step to improve our medical management of this disease in the future.

Key words: Hypoparathyroidism, PTH, Hypocalcemia, hyperphosphatemia

Introduction

Hypoparathyroidism is a rare disorder characterized by hypocalcemia and hyperphosphatemia due to absent or inadequate parathyroid hormone (PTH) secretion (1). The unintentional surgical damage of the parathyroid glands is the most common form, occurring in approximately 78 % of cases (1). Definitive postsurgical hypoparathyroidism is diagnosed when PTH production is insufficient to maintain normocalcemia six months after the intervention (2). Overall, the incidence of chronic hypoparathyroidism after neck surgery is < 2%, depending on the surgeon's expertise (3). Nonsurgical hypoparathyroidism is attributable to autoimmune, genetic or idiopathic etiologies which typically become manifest in childhood (1). The estimated prevalence varies between 23- 30 per million inhabitants in nonsurgical hypoparathyroidism and 220-250 per million inhabitants in surgical hypoparathyroidism (4-6).

As it is a rare disease, data on quality of life, long term risk of complications and correct clinical management have just started to emerge. What is best known is the spectrum of neuromuscular symptoms related to hypocalcemia: mainly paresthesia, cramps or tetany, but also seizures, bronchospasm, laryngospasm or cardiac rhythm disturbances (1). Fewer data are available regarding consequences in the renal, ophthalmic, and cardiovascular systems, fracture risk, infections and psychiatric conditions. The real prevalence of these complications is not available because systematic screening is scarce worldwide (7).

Consequently, recent management guidelines stress the importance of a better clinical assessment of these patients (7). In addition to the routine biochemical monitoring of serum levels of calcium, phosphate and magnesium, some guidelines recommend a wider screening, as clinically indicated, including annual estimated glomerular filtration rate, renal imaging and 24-hr urinary calcium excretion. These screenings would be aimed at assessing renal insufficiency nephrocalcinosis and nephrolithiasis. Central nervous system imaging would evaluate basal ganglia calcifications- Ophthalmologic exams and frequent quality of life assessment should also be included in the screening (2-7).

Inadequate PTH secretion causes failure to mobilize calcium from bone, reabsorb it from the distal nephron and stimulate renal 1α-hydroxylase activity, leading to hypocalcemia. Therapeutic tools include calcium and vitamin D supplements, active vitamin D (1, 25 (OH) vitamin D or calcitriol), analogues that require liver activation (1α hydroxyvitamin D: alfacalcidol and dihydrotachysterol) and thiazide diuretics (2). Higher calcium requirements may cause hypercalciuria and higher calcitriol doses increase the risk of hyperphosphatemia, so a delicate equilibrium is essential. Therefore, although there is little evidence available regarding how to best treat hypoparathyroidism, current general goals of management are: maintaining serum calcium levels in the lower part or slightly below the lower limit of the reference range, keeping serum phosphate and magnesium levels and 24 hr urinary calcium excretion within range, and calcium–phosphate product below 55 mg^2/dl^2 (2,7-9). A major challenge in hypoparathyroidism patients continues to be the effective therapeutic management of the disease in order to minimize the adverse effects of a life-long treatment.

In 2015, replacement therapy with rhPTH (1-84) was first approved in the United States as a useful therapeutic option for hypoparathyroidism, restricted to those patients who are difficult to manage with conventional therapy (10). A group of experts recommend considering its use based on these clinical criteria: inadequate control of the serum calcium concentration; very high oral calcium/vitamin D requirements (>2.5 g of calcium or >1.5 ug of active vitamin D or >3 ug of the 1-α vitamin D analog), hypercalciuria, kidney stones, nephrocalcinosis or reduced creatinine clearance, hyperphosphatemia and/or calcium-phosphate product that exceeds 55 mg^2/dl^2, gastrointestinal tract disorder with malabsorption and reduced quality of life (2).

This context of unmet needs and knowledge gaps motivated us to analyze and share our experience treating patients with this rare disease. Our primary endpoint was to describe the natural history and clinical characteristics of a group of patients with hypoparathyroidism from seven referral bone centers in Argentina. The secondary endpoint was to describe differences between surgical and **nonsurgical** HP patients and our third endpoint, to analyze the number of patients on inadequate control who would meet experts' indications for considering the use of rhPTH 1-84.

Material and methods

Patients

A retrospective observational analysis of chronic hypoparathyroidism patients from seven specialized centers (Hipopara-Red) from Buenos Aires, Argentina, was carried out. To be included, subjects should have had concurrent measurement of albumin-corrected or ionized serum calcium below the lower limits of the normal range and low or undetectable levels of PTH, on at least two occasions separated by 2 weeks. A duration ≥ 6 months of hypocalcemia was considered for inclusion criteria in surgical hypoparathyroidism. Patients with pseudo hypoparathyroidism were excluded. Each center collected requested data from all patients fulfilling the inclusion criteria from their historic database and its analysis was carried out by a centralized institution. Data of demographics, age at diagnosis, disease duration (period between diagnosis and last visit) and etiology were recorded. Clinical manifestations or complications were registered regarding hypocalcemia requiring hospitalization, neuromuscular manifestations (paresthesias, tetany, muscle spasms or pain and seizures), kidney ultrasound positive findings (stones or nephrocalcinosis), renal insufficiency (defined by creatinine clearance below 60ml/min), basal ganglia calcification, detailed fragility fracture history and cataracts. All the above clinical manifestations or complications were considered positive and included in the analysis, if present at least once during follow- up**.** Most recent biochemical parameters available in medical records included serum calcium (mg/dl), ionized calcium (mg/dl), serum phosphorus (mg/dl), calcium-phosphate product (mg^2/dl^2), PTH (pg/ml), serum 25-hydroxyvitamin D (ng/ml), 24-hr-urine calcium and serum magnesium (mg/dl). In most patients, baseline parameters were not available for analysis. Most recent DXA values and treatment regimens (type and doses) were also collected. According to the WHO criteria, osteoporosis was defined as a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of <-2.5 SD). In women prior to menopause and in males younger than age 50, a Z-score of -2.0 or lower was defined as osteopenia (11).

Differences between surgical and nonsurgical hypoparathyroidism regarding demographics, clinical manifestations, biochemical parameters, DXA values and treatment were analyzed.

The study was conducted according to the Helsinki Declaration and was approved by a local ethics committee. Each participant was identified by a number to ensure confidentiality.

Data analysis

Data were expressed as mean ± SD and the Shapiro-Wilk and Bartlett tests were used to assess normality and equal variances respectively. The Student's t test or Mann-Whitney test was used as appropriate to compare surgical and **nonsurgical** groups. Differences were considered significant if $p < 0.05$. Statistical analyses were performed with STATISTIX 7.0 Copyright ©1995, 2000 Analytical software (Statsoft). The association between each complication and possible associated factors was evaluated using univariate logistic regression. The contingency tables were analyzed **using Fisher's test**.

Results

Demographics

A total of 322 subjects with chronic hypoparathyroidism were included, 276 (85.7 %) were female and 46 (14.3 %) male (female/male ratio 6:1). The mean age at the last visit was 55.2 ± 16.8 years; only three subjects were younger than 18 years of age (0.9 %). The mean age at diagnosis was 43.8 ± 16.8 years; disease duration (median time between diagnosis and last visit) was 10.9 ± 9.9 years (Table 1). This database included all subjects followed up between 1985 and December 2018 in Buenos Aires, capital city of Argentina. Last follow-up visit date ranged from December 2002 to November 2018.

Etiology

The majority of patients had surgical hypoparathyroidism (90.7 %, n=292; 258 female and 34 male) mainly due to thyroid carcinoma (45.6 %), benign thyroid adenoma (37.3 %), parathyroidectomy (5.6 %) and other neck surgeries (2.2 %). Benign thyroid adenoma implied benign thyroid disease including single adenoma, goiter, multinodular goiter or Graves' disease. **Nonsurgical**

hypoparathyroidism represented the remaining 9.3 % (n=30, 18 female and 12 male): idiopathic (5 %), autoimmune (2.8 %) and Di George (1.5 %). See figure.

In a sub- analysis of patients who had undergone thyroid surgery of benign and malignant etiologies, we noticed a significant trend over the years. Before 2010, 49.6 % of our patients became hypoparathyroid following a surgery to remove a benign thyroid adenoma. After 2010, hypoparathyroidism secondary to surgery for benign thyroid disease went down to 37.2 % (p= 0.0330).

Clinical manifestations and complications

Paresthesias were found in 31.3 %, tetany in 14.2 %, muscle spasms in 13.3 %, and muscle pain in 6.8 %; 40.9 % reported at least one neuromuscular symptom.

A history of **hypocalcemia requiring hospitalization** was present in 25.7 % (n=83) and fourteen patients (4.3 %) had a history of seizures. These two events were related; seizures were significantly associated with hospitalization for hypocalcemia (p=0.017). Also, **seizures** were positively associated with hyperphosphatemia, elevated calcium-phosphate product and higher doses of calcium supplementation (p= 0.019, 0.020 and < 0.0001, respectively). Basal ganglia calcifications were present in 5/14 patients with a history of seizures, although only 8/14 had been screened using central nervous system imaging. (Table1). Out of all the participants (n=322), basal ganglia calcifications were present in 23 patients. Although it is worth noting that the screening rate was very low, only 59/322 had had undergone nervous system image screening. Patients with basal ganglia calcifications without seizures did not have any other neurological problems, at least reported in this data base, except for paresthesias, muscle spasms or tetany, which as a whole, were **present in 83.3%.**

Kidney assessment by renal ultrasound was performed in 41.9 % (135/322) and 15.5 % (21/135) had positive findings (**kidney stones** (n=15); **nephrocalcinosis** (n=6)). Creatinine clearance calculation was available in 277 patients and was below the normal range (less than 60 ml/min/1.73 m^2) in 62

patients (22.4 %). **Renal insufficiency** was significantly associated with age ($p < 0.0001$): 2/50 (4 %) in patients younger than 39, 17/106 (16 %) in patients between 40 and 59 years of age, 25/95 (26. 3 %) in patients between 60 and 79 and 18/26 (69.2 %) in patients older than 80. Patients older than 60 years of age had 2.9-fold more risk than those younger than 60 to have creatinine clearance below 60ml/min (Odds ratio: 2.918; 95 % confidence interval: 1.617 to 5.263)

Regarding **fracture history**, only nontraumatic fractures were included and were present in 4.9 % of our group: a total of 17 fractures (4 hip, 1 fibula, 2 humerus, 1 rib, 3 vertebrae and 6 wrists) in 14 patients, mean age 71.2 years, range 23 to 94 years. All fractured patients were female, except for a 23-year old male with Di George Syndrome diagnosed with celiac disease after bilateral hip fracture. Apart from this young man, the other youngest patient was a 50-year-old woman with a history of hyperparathyroidism and premature ovarian failure who fractured her wrist. All the other fractured patients were older than 60 years old. As regards hypoparathyroidism etiology, 78.5 % (11/14) were postsurgical, one had Di George and two were idiopathic. Disease duration ranged between 7 and 44 years. Vertebral fractures (N=3) were clinical and confirmed by X-ray, associated with osteopenia or osteoporosis, and present in patients older than 80.

Only 3.4 % (n=11) reported a history of **cataracts,** mean age was 64±19.5 (22-87 years), with a mean disease duration of 20.2±11.9 years (5-38 years). Mean phosphorus level was 4.7±0.8 mg/dl (upper limit of the normal range). In this group, 8/11 patients had a surgical etiology (mean age 78) and three **nonsurgical** (mean age 43). The youngest woman with cataracts was 22 years old, had a five-year autoimmune hypoparathyroidism, hyperphosphatemia, basal ganglia calcifications and a history of multiple hospitalizations for hypocalcemia.

Biochemical parameters

Data for serum calcium were available in 99.3 % and mean calcium level was 8.4 ± 0.8mg/dl; 46 % were below the lower limit, 53.6 % within normal range and only one patient had hypercalcemia (table 2). Plasma phosphate values were available in 95.4 %; only one patient was below the lower limit, 57.3 % within normal range and 42.1 % above normal range. Elevated calcium-phosphate

product (>55 mg^2/dl^2) was present in 1.2 %. Mean serum PTH levels were low (13.4 ± 10.8 pg/ml) and clearly inadequate for serum calcium values. Serum 25-hydroxyvitamin D levels were available in 46 %, 50.7 % were higher than 30 ng/ml, 30.4 % between 20 and 30 ng/ml and 18.9 % under 20 ng/ml. Urinary 24-hr calcium excretion was available in 58.4 % and 49.4 % of those screened had values above the gender reference range.

Serum magnesium levels were available in 80.1 % (n =247) and were lower than the reference range in 24.3 % of patients. Only one patient had values above the normal range. The rest (75 %) were within the reference range but in the medium or lower tertile of normal range. Remarkably, half of the patients with serum magnesium levels in the lower tertile were receiving supplements.

DXA values

Lumbar spine and hip DXA assessment was performed in 38 % (123/322) of the patients. Mean lumbar spine T-score was -0.3 ± 1.9, mean femoral neck T-score was -0.3 ± 1.5 and mean total hip T-score -0.2 ± 1.3. There were not significant differences in T-score or Z-scores values between postsurgical or **nonsurgical** patients (data not shown). Although mean values were within the normal range, 48/123 (39 %) had osteopenia and 16/123 (13 %) had osteoporosis.

Treatment

The decision on treatment election was made by the patient´s endocrinologist. Most patients were receiving calcium supplements (mean dose 2019 ± 1426 mg/day, expressed as elemental calcium) plus calcitriol (mean dose 0.498 ± 0.279 ug/day) and 22.9 % were receiving diuretics (hydrochlorothiazide (16 %), indapamide (3.7 %)) (table 2). More than half (54.3 %) were receiving vitamin D supplementation.

Fourteen patients (4.3 %) were receiving PTH supplementation, 13 female and one male; median age was 49.57 (18- 88 years) and median time since diagnosis was 9 years. Thirteen were receiving rhPTH 1-34 and one rhPTH 1-84. These patients had a history of frequent intravenous calcium administration and episodes of life-threatening severe hypocalcemia. Thirteen were **postsurgical** and one idiopathic. Most were still requiring calcium supplements (1792 mg/day) and calcitriol

(0,51ug/day). It is important to clarify that these off-label rhPTH 1-34 treatments were started before rhPTH 1-84 was available and approved for hypoparathyroidism.

Differences between surgical and nonsurgical HP patients

Nonsurgical hypoparathyroidism subjects were younger and diagnosed at a younger age; female/male ratio was more balanced: 60 % were women (table 1). A history of severe hypocalcemia, paresthesias, tetany and muscle spasms was significantly more frequent in **nonsurgical** patients. Ganglia calcifications, seizures and cataracts were significantly higher. There were no differences regarding renal complications, biochemical parameters, DXA values or treatment characteristics (Table 1 and 2).

Candidates who met experts' indications for considering the use of rhPTH 1-84

According to the international guidelines, 210 of our patients met experts' indications for considering the use of rhPTH 1-84 . If we add the fourteen that were already receiving it, the number rises to 69.5 % (n=224) of our group (2) (Table 3). Hyperphosphatemia would be the indication for the majority (n=124), daily oral calcium requirements exceeding 2.5 g of calcium in 74, and only one because of >1.5 µg of active vitamin D. Inadequate control of the serum calcium concentration was the reason why fourteen patients were already under rhPTH 1-34 or rhPTH 1-84. In the remaining cases, the patients presented hypercalciuria, kidney stones, nephrocalcinosis, or reduced eGFR. (See detailed numbers in table 3). Quality of life was not evaluated so it could not be used as an indication criterion. (or could not be considered within the indication criteria)

Discussion

In this observational retrospective cross-sectional study, we described the natural history of 322 subjects with hypoparathyroidism. We found a higher prevalence of **postsurgical** etiology (90.7 %) compared with the prevalence described in the literature (67 -78 %) (1, 2, 6). This could be attributed to the fact that our centers mainly treat adults, so we do not usually see pediatric patients who might have contributed with more nonacquired etiology.

Most of our patients were premenopausal women, whose diagnosis was made after a thyroid surgery, what is consistent with the prevalence of thyroid nodular disease. Regrettably, almost 40 % suffered this life-long condition after a surgery for a benign thyroid disease. The extents of the surgery, central compartment node dissection and reoperation have been described as risk factors for developing hypoparathyroidism (12). We had no data on the type of surgical procedure but, fortunately, after 2010 we observed a significant decrease in the number of patients becoming hypoparathyroid after a surgery for benign thyroid disease.

History of severe hypocalcemia requiring hospitalization was present in one out of four; and less severe hypocalcemia was responsible for at least one neuromuscular symptom, this being reported in 40 %. The prevalence of seizures was similar to that described in the literature (4- 8 %) and it was clearly more prevalent in **nonsurgical** patients (3).

Concern has been raised regarding renal impairment as higher risk of kidney stones, nephrocalcinosis, renal insufficiency and even dialysis **have** been described (4). Kidney stones or nephrocalcinosis were found only in 15.5 % of our group, probably because less than half of our patients had had a renal ultrasound performed. A high prevalence of nephrocalcinosis (12 to 57 %) and a hazard ratio for developing kidney stones of 4.82 (95 % CI: 2.00–11.64) was reported in patients with hypoparathyroidism who **were** treated with calcium and activated vitamin **D** (4,13).Renal insufficiency, defined by creatinine clearance below 60ml/min, was present in 22.4 % of our patients and it was significantly associated with age, ranging from 4 % in younger than 39- year-olds to 69.2 % in patients older than 80. This prevalence is higher than expected for our general population; in a study done on 88,500 blood and urine samples in Buenos Aires, the authors reported a prevalence of 12 % (14). Impaired renal function has been associated with age, duration of the disease and relative time with hypercalcemia (15). Two-thirds of subjects included in an early intervention trial had decreased creatinine clearance values at baseline, and 40 % had verified renal calcinosis (16). In a US cohort, 41 % of patients had an eGFR < 60 ml/min/1.73 m^2, which was between 2–17-fold higher than age-adjusted normal values (15). In two Danish case-control studies,

the hazard ratios for renal insufficiency were 3 (95 % CI: 1.73–5.55) and 6 (95 % CI: 2.45–14.75) for patients with surgical and **nonsurgical** hypoparathyroidism, respectively, compared with age-matched controls (4, 17)

Data on fracture risk among patients with this disorder vary. In some postsurgical hypoparathyroid cohorts, patients may have a decreased risk of fracture in the upper extremities, whereas others show an increased risk of vertebral fractures despite having normal or increased bone mineral density (18-21) **Nontraumatic** fractures were present in 5 % of our group and almost all had happened in aged postmenopausal women. Although there are no published data on the general incidence of fragility fractures in our country, prevalence of asymptomatic vertebral fractures in Argentinian women aged 50 was estimated in 16.19 % in the LAVOS´S study (22).

In our group, 42 % had serum phosphate levels above the reference range. Underbjerg et al. recommend that serum phosphate in this population should be kept in the lower part of the reference interval, because higher phosphate levels are associated with increased mortality and risk of infections (17). Unfortunately, in our patients, lowering serum phosphate seems to be one of the most challenging tasks.

In Argentina, we tend to favor calcium over active vitamin D use: mean calcium elemental requirements were around 2000 mg/day and calcitriol 0.5 ug/day. This perspective is similar to the US experience and different from the European, which focuses more on the 1-alpha analogue of vitamin D than on supplemental calcium. Fourteen patients were receiving PTH supplementation: thirteen with rhPTH 1-34 and one with rhPTH 1-84. These patients had previously had more frequent hospitalizations, more severe hypocalcemia, higher serum phosphate and calcium urinary excretions and higher calcium and calcitriol requirements than a control group of patients receiving standard treatment (23). With PTH supplementation, their serum calcium levels improved and calcium and calcitriol requirements decreased and became similar to those of the conventionally treated group.

As expected and previously reported, **nonsurgical** hypoparathyroidism subjects were younger and had been diagnosed at an earlier age; besides, the number of female patients was lower (5; 24).

Overall, they seem to have more complications, especially those related to hypocalcemia such as neuromuscular symptoms, cataracts, basal ganglia calcifications and seizures (5). Underberj et al. found that these patients had a significantly increased risk of renal insufficiency ([HR] 6.01), cardiovascular diseases (HR 1.91), neuropsychiatric complications (HR 2.45), infections (HR 1.94) and fractures at the upper extremities compared with a control group (5).

According to the experts' indications, 210 of our patients might be eligible for the use of rhPTH, although it is not yet commercially available in Argentina (2). However, these indications are not strict evidence-based recommendations but rather guidance to consider treatment with f rhPTH 1-84. We were surprised and worried about the high percentage of patients with inadequate control, especially patients with hyperphosphatemia and renal complications. This high number might partially be explained by the significant percentage of patients older than 60 years of age and even older than 80 with renal insufficiency.

We are aware that due to the retrospective design of our study, the prevalence of acute and chronic complications is probably underdiagnosed in our patients. Less than half of our patients met the screening recommendations for renal ultrasound, 24-hr urine calcium excretion and central nervous system imaging **assessment, which probably** underestimated the prevalence of basal ganglia calcifications, nephrocalcinosis, hypercalciuria and kidney stones. Also, we only recorded self-reported cataracts. We were not able to evaluate quality of life, fatigue, lack of concentration, depression, and other neuropsychiatric issues. Other limitations of this study are that the participating centers were almost exclusively for adults, which exaggerates surgical etiology, and the lack of genetic testing for the diagnosis of **nonsurgical** cases. Moreover, all centers were from the capital city, Buenos Aires, and it is uncertain whether these data can be extrapolated to the whole Argentinian population. Patients in our cohort were evaluated at reference centers and thus, they might have been more severely affected with a higher rate of complications than the overall population (referral bias). Finally, the results of laboratory values over a time span and from different facilities might be affected by changes in assay technology and performance.

That being said, our results were generally consistent with peer-reviewed reports. The main strengths of this study are the large number of patients included, the long follow-up period and the complete biochemical profile. In addition, according to our knowledge, this is the first study on hypoparathyroidism in Argentina and Latin America.

As a conclusion, analyzing our experience, we have learned several lessons. Despite being followed up by experienced physicians, clinical management and monitoring were heterogeneous and probably insufficient to assess all the potential complications. Hyperphosphatemia was present in a high proportion of our patients and more than half might have been eligible to receive treatment with rhPTH 1-84 . Being aware of our current management of this rare disease is the first step to improve our clinical approach in the future. Longitudinal prospective studies including the whole country are necessary to permit a better understanding of the clinical manifestations, short- and long-term complications and therapeutic challenges of these patients.

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Data Availability

Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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Tables and figures

Table 1. Demographic data and clinical characteristics of the whole group, surgical and nonsurgical subgroups

	All (n=322)	**Surgical (n=292)**	**Non-surgical (n=30)**	**p**
Demographics	n (%)			
Age (years)	54.3 ± 16.8	55.4 ± 16.1	43.3 ± 18.9	**0.0003**
Female	276 (85.7 %)	258 (88.3 %)	18 (60 %)	**0.0002**
Age at diagnosis	43.8 ± 16.8	45 ± 15.9	31.4 ± 20.5	**<0.01**
Disease duration (years)	10.9 ± 9.9	10.7 ± 10	12.5 ± 9.5	0.25
Clinical Manifestations (%)				
Severe hypocalcemia	83 (25.7)	68 (23.2)	15 (50)	**0.003**[†]
Paresthesias	101 (31.3)	84 (28.7)	17 (56.6)	**0.003**[†]
Tetany	46 (14.2)	35 (12)	11 (36.6)	**0.001**[†]
Muscle spams	43 (13.3)	35 (12)	8 (26.6)	**0.042**[†]
Muscle pain	22 (6.8)	19 (6.5)	3 (10)	0.444[†]
Seizures	14 (4.3)	7 (2.3)	7 (23.3)	**<0.0001**[†]
eGFR <60 [n (%)]	62 (22.4)	58 (23)	4 (16)	0.42[†]
Lithiasis/nephrocalcinosis	21/135 (15.5)	19/117 (16.2)	2/18 (11.1)	0.738[†]
Basal ganglia calcification	23/59 (38.9)	14/46 (30.4)	9/13 (69.2)	0.021[†]
Fracture history	14 (4.3)	11 (3.8)	3 (10)	**0.131**[†]
Cataracts	11 (3.4)	8 (2.7)	3 (10)	0.072[†]

[†]Two-Sample Proportion Test. Severe hypocalcemia is defined as hypocalcemia requiring hospitalization

Table 2: Biochemical parameters and treatment characteristics of the whole group, surgical and nonsurgical subgroups

Biochemical parameters (Normal range)	**All (n=322)**	**Surgical (n=292)**	**Nonsurgical (n=30)**	**p**
Calcium (8.5-10.5 mg/dl)	8.4 ± 0.8	8.4 ± 0.8	8.4 ± 0.9	0.51[&]
Ionized calcium (4.1-5.2 mg/dl)	4.2 ± 0.5	4.3 ± 0.5	4.1 ± 0.6	0.17[&]
Albumin (3.2-4.8 g/l)	4.1 ± 0.4	4.1 ± 0.4	4.3 ± 0.4	0.14[&]
Phosphorus (2.5-5 mg/dl)	4.7 ± 0.9	4.7 ± 0.9	4.9 ± 1.0	0.12[&]
PTH (10-65 pg/ml)	13.4 ± 10.8	13.5 ± 10.9	11.7 ± 9.6	0.47[&]
25-hydroxyvitamin D (30ng/ml)	34.9 ± 13.2	34.3 ± 13.1	42.6 ± 13.5	**0.029**[&]
Magnesium (1.9-2.5 mg/dl)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.66[&]
Urine calcium (220 mg/24hr)	201.5 ± 131.9	198.5 ± 134.4	228.2 ± 105.6	0.16[&]
Hypercalciuria (%)	98/174 (56.3)	87/156 (55.7)	11/18 (61.1)	0.803 [†]
Creatinine (0.6-1.1 mg/dl)	0.93 ± 0.54	0.93 ± 0.54	0.94 ± 0.52	0.88[&]
eGFR (≥60ml/min/1.73 m^2)	76.0 ± 24.8	74.8 ± 23.5	88.2 ± 34.2	0.07
Treatment (doses)				
Calcium (mg/day)	2019 ± 1426	2033 ± 1447	1876 ± 1232	0.67
Calcitriol (ug/day)	0.498 ± 0.279	0.491 ± 0.275	0.566 ± 0.321	0.26
Magnesium (mg/day)	328 ± 368	316 ± 366	415 ± 381	0.23

Thiazides (mg/day)	30.8 ± 21.4	32.7 ± 22.0	16.2 ± 5.9	0.17
Vitamin D (thousand IU/week)	28.1 ± 22	27.6 ± 22	33.3 ± 26	0.37

Abbreviations: PTH: parathormone; eGFR: estimated glomerular filtration rate;

#Unequal variances. & Non-parametric distribution. † Two-Sample Proportion Test. We provide t and z-scores for all patients (n=123), although T-score (<-2.5 SD) was used in postmenopausal women and men older than 50 and Z-score in women prior to menopause and in males younger than age 50 (≤ -2.0) to define osteoporosis or low bone mass, respectively. Vitamin D was both ergo or cholecalciferol. Patients receiving rhPTH 1-84 or rhPTH 1-34 (n=14) were excluded from the biochemical analysis in this table.

Table 3. Indications for considering the use of rhPTH 1-84 in our patients (2). Several patients fulfilled more than one of the criteria. The 14 patients already with rhPTH 1-84 or rh PTH 1-34 were the ones with inadequate control of the plasma calcium concentration.

Indications for Considering the Use of rhPTH	Number of patients
Inadequate control of the plasma calcium concentration	14 (4.34%)
Oral calcium that exceeds 2.5 g of calcium ≥1.5 ug of calcitriol	74 (22.9%) 1 (0.3%)
Hypercalciuria Kidney stones Nephrocalcinosis Reduced clearance (≤60 mL/min)	98 (30.43%) 15 (4.65%) 6 (1.86%) 62 (19.25%)
Hyperphosphatemia and/or calcium-phosphate product Exceeding 55 mg^2/dL^2 (4.4 $mmol^2/L^2$)	124 (38.55)
Total patients (Several fulfilled ≥ 1 criteria)	224 (69.5%)

Figure legend:

Etiology in 322 patients with hypoparathyroidism. Thyroid adenoma implies benign thyroid disease including single adenoma, goiter, multinodular goiter or Graves' disease.