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Long-term renal and systemic outcomes in chronic hypoparathyroidism under conventional therapy: a multicenter cohort study

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Research Article

Keywords: Hypoparathyroidism, Chronic kidney disease, Calcium metabolism, Conventional therapy, Long-term outcomes

Posted Date: June 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9666675/v1

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Additional Declarations: No competing interests reported.

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Abstract

Purpose

To evaluate long-term clinical outcomes and systemic complications in patients with chronic hypoparathyroidism (HP) managed with conventional therapy at tertiary endocrinology centers.

Methods

This retrospective multicenter cohort study included patients followed at four endocrinology referral centers in the state of Rio de Janeiro, Brazil, between 2018 and 2021. Demographic, clinical, laboratory and therapeutic data, as well as complications, were evaluated. Data are presented as n (%) or median and interquartile range (p25–p75).

Results

A total of 113 participants were included, predominantly women (93.8%), with a median age of 46 years (37–56) and a median disease duration of 7.5 years (4–15). Postsurgical HP was predominant (93.8%), most commonly following surgery for nontoxic multinodular goiter (63.8%). Conventional therapy was associated with improvement in serum calcium levels ($p<0.001$) and reduction in serum phosphate levels ($p<0.001$). A significant decline in estimated glomerular filtration rate (eGFR) was observed over follow-up (93.1 vs. 81.1 mL/min/1.73m²; $p<0.001$), with chronic kidney disease (CKD) progression in 32.3% of participants. Advanced CKD stages were strongly associated with systemic arterial hypertension (SAH) ($p<0.001$) and diabetes mellitus (DM) ($p=0.001$). Osteopenia was more prevalent among participants with CKD progression (24.1% vs. 5.0%; $p=0.018$).

Conclusion

Although conventional therapy promotes adequate metabolic control, clinically relevant complications persist in a substantial proportion of patients — most notably a progressive decline in renal function, affecting nearly one-third of the cohort. These findings underscore the importance of rigorous long-term monitoring and raise concerns regarding the ability of current management strategies to prevent progressive organ damage in chronic HP.

Keywords: Hypoparathyroidism, Chronic kidney disease, Calcium metabolism, Conventional therapy, Long-term outcomes

Introduction

Hypoparathyroidism (HP) is defined by absent or insufficient parathyroid hormone (PTH) secretion, resulting in hypocalcemia, hyperphosphatemia, and hypercalciuria [1]. Estimated prevalence ranges from 23 to 37 cases per 100,000 inhabitants in the United States, Denmark, and Italy; no population-based data exist for Brazil or most of Latin America [2].

Approximately 80% of HP cases arise following cervical surgery with inadvertent removal or injury of the parathyroid glands; the remaining 20% are attributable to autoimmune, genetic, infiltrative, or metabolic causes [1]. Clinical presentation varies widely, ranging from mild paresthesia to tetany, laryngospasm, and seizures [3]. Long-term complications include renal, skeletal, cardiovascular, and neuropsychiatric manifestations, as well as impaired quality of life [3, 4].

First-line therapy consists of oral calcium supplementation and active vitamin D analogues, with thiazide diuretics used adjunctively in selected cases [4, 5]. The therapeutic goal is to maintain serum calcium within the low-normal range, thereby limiting hypercalciuria and its renal consequences [5]. However, conventional therapy carries important limitations. From a practical standpoint, patients frequently face complex dosing regimens and unpredictable fluctuations in serum calcium levels. From a clinical standpoint, long-term use has been associated with progressive increases in urinary calcium and serum phosphorus, as well as adverse renal outcomes — including nephrolithiasis, nephrocalcinosis, and chronic kidney disease (CKD) — and reduced health-related quality of life [5–7].

Despite growing recognition of these complications, significant gaps remain in the literature, particularly regarding HP in Latin America. No population-based studies have documented the prevalence or incidence of HP in Brazil, and the long-term evolution of complications among patients receiving conventional therapy remains poorly characterized in Brazilian cohorts. These gaps highlight the need for real-world data from this population. Therefore, the present study aims to determine the clinical outcomes and long-term complications of patients with chronic HP undergoing conventional therapy and followed up at endocrinology outpatient clinics of tertiary referral hospitals in the Metropolitan Region of Rio de Janeiro.

Methods

Study Design

This was a retrospective cohort study conducted at four tertiary endocrinology referral centers in the state of Rio de Janeiro, Brazil: Hospital Universitário Antônio Pedro (HUAP-UFF), Hospital Federal dos Servidores do Estado (HFSE), Hospital Universitário Pedro Ernesto (HUPE-UERJ), and Instituto Estadual de Diabetes e Endocrinologia Luiz Capriglione (IEDE). Data were obtained through the review of medical records, with data collection spanning the period from 2018 to 2021.

Given the retrospective and exploratory nature of this study, a formal sample size calculation was not performed; the sample comprised all eligible patients identified at the participating centers during the study period.

Ethical Approval

The study was approved by the Research Ethics Committees of all four participating institutions (HUAP-UFF CAAE: 82845317.0.0000.5243; HFSE CAAE: 82845317.0.3001.5252; HUPE-UERJ CAAE: 82845317.0.3002.5259; IEDE CAAE: 82845317.0.3003.5266). All participants provided written informed consent prior to enrolment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Participants

Participants were selected by non-probabilistic convenience sampling from outpatient endocrinology clinics at the participating centers. Inclusion criteria were: age ≥18 years, HP diagnosis for at least six months, and regular follow-up at a participating center, with no more than 24 months between consecutive visits. Patients were excluded if they had: (1) CKD and had undergone parathyroidectomy for secondary or tertiary hyperparathyroidism. (2) a history of renal transplantation; or (3) chronic use of nephrotoxic agents that could independently account for renal function decline.

Variables and Definitions

Data were extracted through standardized manual review of medical records, including clinical notes, laboratory results, and imaging reports. Variables were organized across three time points.

1. Initial Assessment (IA): Defined as the first documented outpatient visit or, where available, data from the time of HP diagnosis. The following variables were collected:

Demographic and clinical data included age (years), sex, weight (kg), height (m), and body mass index (BMI, calculated as weight/height^2). HP etiology was classified as postsurgical or non-surgical. Postsurgical HP was further characterized by surgical indication (total thyroidectomy, partial thyroidectomy, parathyroidectomy, or other cervical surgery) and time elapsed since surgery (years). Non-surgical HP was classified as autoimmune, genetic, idiopathic, or other. Comorbidities recorded at IA included systemic arterial hypertension (SAH; defined by prior diagnosis or use of antihypertensive agents), diabetes mellitus (DM; type 1 or 2, per medical documentation and treatment), dyslipidemia (prior diagnosis or use of lipid-lowering agents), and cardiovascular disease (CVD; history of acute myocardial infarction, angina, stroke, or peripheral arterial disease).

Biochemical parameters collected at IA included: albumin-corrected total calcium (CaTC), calculated as CaTC = measured Ca + [0.8 × (4.0 − albumin)] (mg/dL); intact PTH (pg/mL); serum phosphate (mg/dL); serum magnesium (mg/dL); 25-hydroxyvitamin D [25(OH)D] (ng/mL); serum creatinine (mg/dL); estimated glomerular filtration rate (eGFR), estimated by the CKD-EPI 2021 equation [8] and expressed in mL/min/1.73m^2; and 24-hour urinary calcium excretion, expressed both in mg/24h and in mg/kg/24h. Hypercalciuria was defined as urinary calcium excretion >4 mg/kg/24h, in accordance with established clinical thresholds. CKD was staged according to KDIGO 2024 criteria [9]: stage 1, eGFR ≥90; stage 2, eGFR 60–89; stage 3, eGFR 30–59; stage 4, eGFR 15–29; stage 5, eGFR <15 mL/min/1.73m^2. History of low-impact fracture (fracture caused by minimal trauma or a fall from standing height) and bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) were also recorded when documented.

2. Follow-up Data: Complications. The following complications were recorded at any point during the follow-up period: nephrolithiasis (diagnosed by ultrasound, computed tomography, or documented spontaneous stone passage); nephrocalcinosis (parenchymal renal calcifications on imaging); basal ganglia calcifications (BGC; calcifications in the basal nuclei on CT or MRI of the skull); ectopic calcifications in other soft tissues (documented by imaging); posterior subcapsular cataract (confirmed ophthalmological diagnosis); low-impact fractures occurring during follow-up; positive Trousseau's and/or Chvostek's signs documented during consultations in the setting of normal serum calcium; and changes in BMD on serial DXA

(where available). Comorbidities including DM, SAH, CVD, dyslipidemia, and hypercalciuria were also recorded throughout follow-up.

3. Final Assessment (FA): Defined as data from the last documented visit within the study period. Variables collected included age (years), weight (kg), height (m), BMI (kg/m²), and self-reported ethnicity (White; non-White, comprising Black and mixed-race [pardo]; indigenous; or Asian). Total follow-up time at the service (years) was also recorded. Biochemical parameters repeated at FA included CaTC, serum phosphate, magnesium, 25(OH)D, creatinine, eGFR, CKD stage, 24-hour urinary calcium (mg/24h and mg/kg/24h), and the calcium-phosphate product (mg/dL). CKD progression was defined as advancement by at least one KDIGO stage between IA and FA. Pharmacological data collected at FA included current medications and doses of elemental calcium (mg/day), calcitriol (µg/day), cholecalciferol (IU/day), and thiazide diuretics (mg/day).

Statistical Analysis

Data were managed using Microsoft Excel and analyzed using R software (version 4.5.1; R Core Team). Categorical variables are presented as absolute (n) and relative (%) frequencies and continuous variables as median and interquartile range (p25–p75). Pearson's chi-square test was used for comparisons between categorical variables. Welch's t-test or the Wilcoxon/Mann-Whitney test was used for comparisons between continuous and categorical variables across two groups, depending on the normality of distribution assessed by Shapiro-Wilk test. The Kruskal-Wallis test was used for comparisons involving three or more groups, and Spearman's correlation coefficient for associations between continuous variables. Statistical significance was set at $p<0.05$.

Results

- **Clinical and Epidemiological Profile**

A total of 113 participants were included. The majority were women (93.8%), with a median age at diagnosis of 46 years (37–56) and a median disease duration of 7.5 years (4–15). Ethnicity was equally distributed between White and non-White participants (50% each; 5 missing records). Postsurgical etiology was predominant (93.8%), followed by pseudohypoparathyroidism (5.3%) and autoimmune HP (0.9%). Among postsurgical cases, the leading indication was nontoxic multinodular goiter (63.8%), followed by thyroid cancer (18.1%), Graves' disease (13.3%), and toxic nodular goiter (4.8%). Median BMI increased

significantly from 26.9 kg/m² (24.0–30.3) at IA to 28.0 kg/m² (25.0–31.7) at FA (p=0.007). Clinical characteristics are presented in Table 1.

Variable	n=113
Age at diagnosis, years	46 (37–56)
Disease duration, years	7.5 (4–15)
Female sex	106 (93.8%)
White ethnicity*	54 (50.0%)
BMI at IA, kg/m²	26.9 (24.0–30.3)
BMI at FA, kg/m²	28.0 (25.0–31.7)†
Etiology	
Postsurgical	106 (93.8%)
Pseudohypoparathyroidism	6 (5.3%)
Autoimmune	1 (0.9%)
Surgical indication	
Nontoxic multinodular goiter	67 (63.8%)
Thyroid cancer	19 (18.1%)
Graves' disease	14 (13.3%)
Toxic nodular goiter	5 (4.8%)

*Data expressed as n (%) or median (p25–p75). IA = initial assessment; FA = final assessment; BMI = body mass index. *5 missing records. †p=0.007 vs. IA.*

Table 1. Clinical and epidemiological profile of participants with hypoparathyroidism on conventional therapy (n=113).

- **Biochemical Parameters**

At HP diagnosis, median PTH was 4.6 pg/mL (3.0–9.7), serum calcium 7.5 mg/dL (6.7–8.2), and phosphate 5.1 mg/dL (4.3–6.0). Conventional therapy was associated with a significant increase in serum calcium (7.5 vs. 8.3 mg/dL; p<0.001) and reduction in serum phosphate (5.1 vs. 4.5 mg/dL; p<0.001). Median eGFR declined significantly from 93.1 mL/min/1.73m² (79.3–109.7) at IA to 81.1 mL/min/1.73m² (68.7–97.6) at FA (p<0.001). No significant changes were observed in serum 25(OH)D, magnesium, calcium-phosphate product, or urinary calcium excretion between assessments. Detailed biochemical data are shown in Table 2.

Parameter	Initial Assessment	Final Assessment
PTH (pg/mL)	4.6 (3.0–9.7)	—
Corrected calcium (mg/dL)	7.5 (6.7–8.2)	8.3 (7.9–8.7)*
Phosphate (mg/dL)	5.1 (4.3–6.0)	4.5 (4.0–5.1)*
Magnesium (mg/dL)	1.8 (1.6–2.0)	1.9 (1.7–2.0)
25(OH)D (ng/mL)	32.7 (25.6–42.1)	34.1 (27.1–48.9)
Ca-P product (mg/dL)	37.6 (32.4–43.8)	38.1 (33.1–41.7)
Urinary Ca (mg/24h)	129.6 (55.1–191.5)	121.1 (61.8–180.4)
Urinary Ca (mg/kg/24h)	1.8 (0.7–3.2)	1.95 (0.9–2.7)
eGFR (mL/min/1.73m²)	93.1 (79.3–109.7)	81.1 (68.7–97.6)*

**p<0.001 vs. initial assessment. eGFR estimated by CKD-EPI 2021. 25(OH)D = 25-hydroxyvitamin D.*

Table 2. Biochemical parameters at initial and final assessment. Data as median (p25–p75).

- **Pharmacological Treatment**

Nearly all participants (95.5%) used elemental calcium supplementation, with 33.6% requiring doses exceeding 2,000 mg/day. Calcitriol was used by 76.9% of participants, cholecalciferol by 45.1%, and both simultaneously by 36.2%; 14.1% used no vitamin D supplementation. Thiazide diuretics were used by 49 (43.4%) of the participants. Of these, 20 (17.7%) were prescribed thiazides solely for SAH, 8 (7%) for both SAH and hypercalciuria, and 4 (3.5%) exclusively for hypercalciuria. Indication data were missing for the remaining 7 participants. Notably, 10 participants (8.8%) were using thiazide diuretics in the absence of either SAH or hypercalciuria, which may reflect undocumented indications or prescribing patterns that warrant further investigation. Participants using thiazide diuretics had significantly lower 24-hour urinary calcium excretion at FA (103.5 vs. 156.0 mg/24h; p=0.036). No significant correlation was observed between the use of elemental calcium, calcitriol, or cholecalciferol and 24-hour urinary calcium excretion. Medication distribution and doses are detailed in Figure 1 and Table 3.

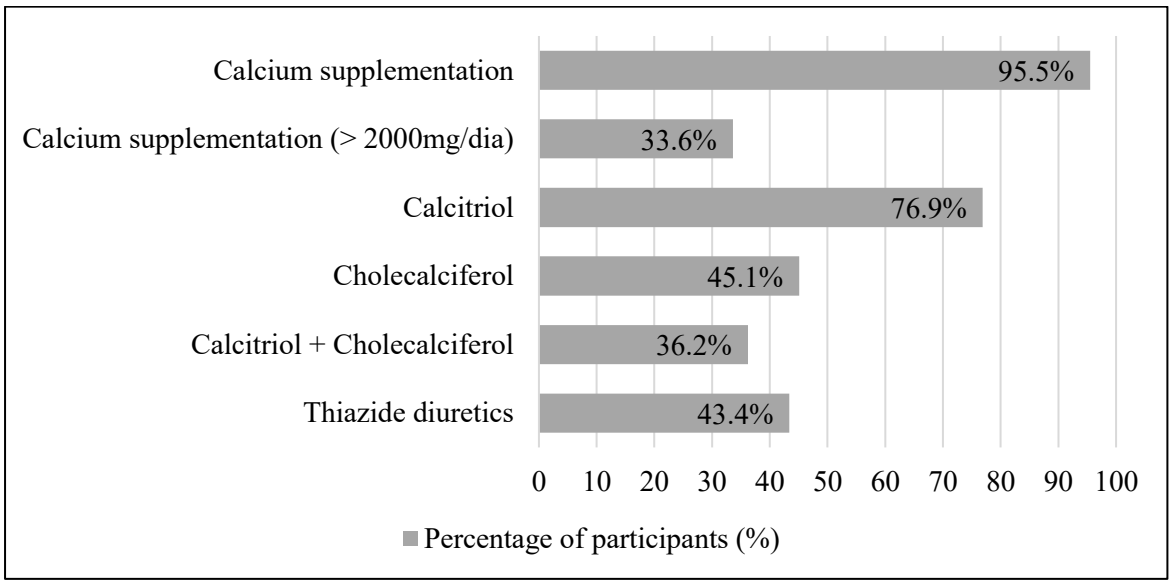


Fig. 1 Distribution of pharmacological treatments used in the conventional management of hypoparathyroidism (n = 113).

Medication	Median	Range (min–max)
Elemental calcium (mg/day)	2000	400–6000
Calcitriol (µg/day)	0.50	0.25–2.0
Cholecalciferol (IU/day)	1600	200–40000
Hydrochlorothiazide (mg/day)	25	12.5–75

Table 3. Doses of medications used in conventional therapy of hypoparathyroidism.

- **Associated Complications**

Among the comorbidities recorded, the most frequent were SAH in 60 (53.1%), dyslipidemia in 40 (35.4%), and DM in 28 (24.8%) (Figure 2). During follow-up, hypercalciuria occurred in 17 (15%) individuals at some point during data collection, nephrolithiasis in 10 (8.8%), cataract in 5 (4.4%), and CVD in 3 (2.7%). Trousseau's sign in the context of normal serum calcium was documented in 7 participants (6.3%), and Chvostek's sign under the same conditions in 4 (3.6%); BGC was identified in 6 (5.3%).

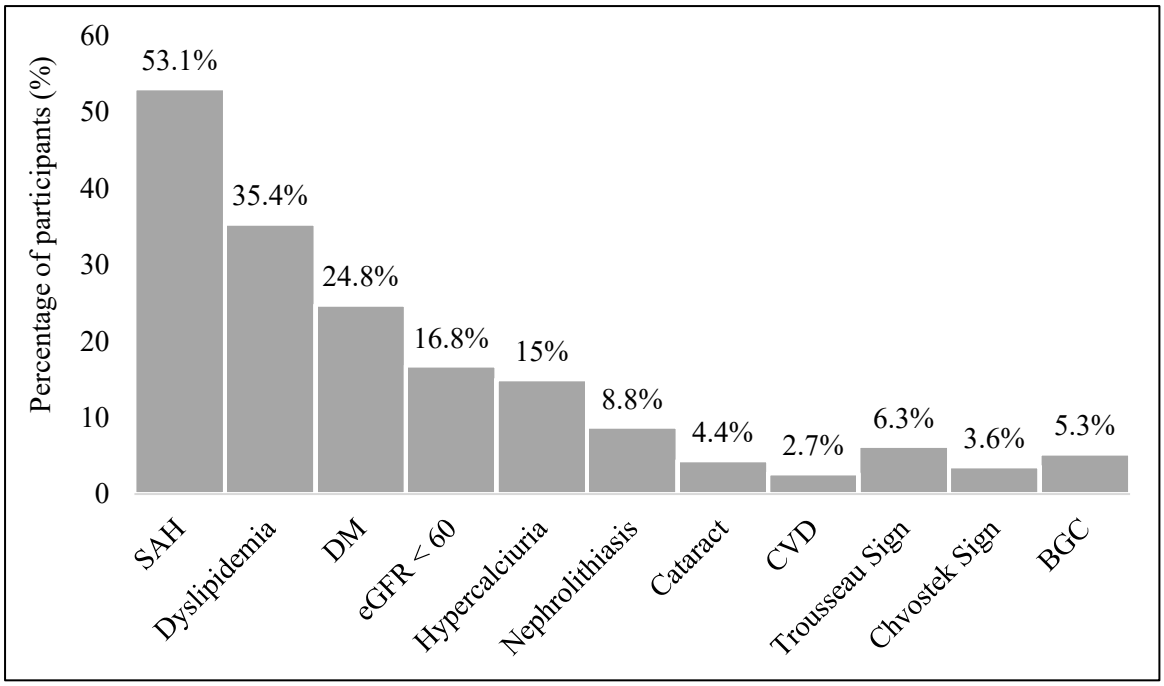


Fig. 2 Prevalence of comorbidities in patients with chronic hypoparathyroidism receiving long-term conventional therapy (n = 113).

A significant difference was observed in CKD stages at the time of HP diagnosis versus FA data ($p < 0.001$). As shown in Figure 3, an increase in the proportion of individuals in more advanced CKD stages was observed, including one participant whose eGFR declined to levels below 30 mL/min/1.73 m². Furthermore, progression of CKD stage was observed in 32.3% of participants, and a prevalence of 16.8% of individuals with eGFR below 60 mL/min/1.73 m² was identified.

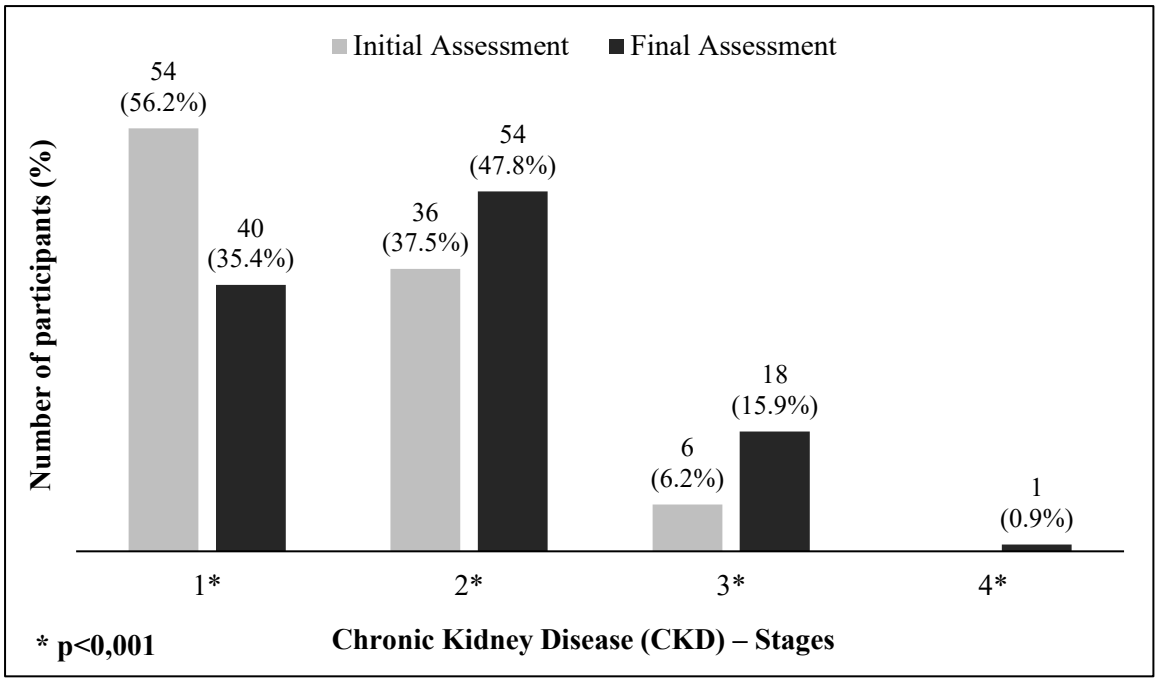


Fig. 3 Changes in chronic kidney disease (CKD) stages from baseline to final assessment in 113 patients with chronic hypoparathyroidism.

At FA, a higher prevalence of SAH and DM was observed among participants in more advanced stages of CKD ($p < 0.001$ and $p = 0.001$, respectively). As shown in Table 4, among participants with stage 3 CKD, 88% had SAH and 61.1% had DM.

CKD Stage	Without SAH	With SAH	Without DM	With DM
1 (n=40)	27 (67.5%)	13 (32.5%)	34 (85.0%)	6 (15.0%)
2 (n=54)	24 (44.4%)	30 (55.6%)	43 (79.6%)	11 (20.4%)
3 (n=18)	2 (11.1%)	16 (88.9%)	7 (38.9%)	11 (61.1%)
4 (n=1)	0 (0%)	1 (100%)	1 (100%)	0 (0%)

SAH p<0.001; DM p=0.001 (Pearson chi-square). Values as n (%). CKD = chronic kidney disease.

Table 4. CKD stages and prevalence of systemic arterial hypertension (SAH) and diabetes mellitus (DM) at final assessment.

No association was observed between CKD progression and the calcium–phosphorus product, BMI, or the use of medications for HP treatment (calcium supplementation or calcitriol). Similarly, no significant association was found between the use of these medications, the calcium–phosphorus product, or 24-hour urinary calcium excretion and the occurrence of nephrolithiasis. These findings are presented in Tables 5 and 6.

Parameter	CKD progression (n=31)	No progression (n=65)	p
Ca-P product (mg/dL)	38.59 (33.83–41.27)	38.53 (32.49–43.10)	0.545
BMI (kg/m²)	27.80 (24.31–31.00)	28.60 (26.45–33.40)	0.178
Elemental calcium (mg/day)	2000 (1000–2950)	2000 (1500–3000)	0.125
Calcitriol (µg/day)	0.50 (0.50–0.75)	0.50 (0.25–0.63)	0.067

Data as median (p25–75). Wilcoxon test. Data available for 96 of 113 participants (17 missing records).

Table 5. Metabolic and pharmacological parameters related to CKD progression.

Parameter	Nephrolithiasis (n=10)	No nephrolithiasis (n=103)	p
Ca-P product (mg/dL)	38.10 (33.10–41.70)	38.99 (37.12–40.70)	0.404
Elemental calcium (mg/day)	2000 (1000–3000)	2000 (1000–2000)	0.714
Calcitriol (µg/day)	0.50 (0.25–0.75)	0.50 (0.50–0.75)	0.095
Urinary Ca (mg/kg/24h)	1.96 (0.98–2.69)	1.86 (1.27–3.50)	0.230

Data as median (p25–75). Wilcoxon test.

Table 6. Metabolic and pharmacological parameters related to nephrolithiasis.

- **Bone Health**

Of the 113 participants, 104 had DXA data available. Osteopenia was identified in 10 participants (9.6%), osteoporosis in five (4.8%), and low bone mass for age in four (3.8%). Low-impact fractures occurred in three participants (2.8%); two had DXA findings consistent with osteopenia and one had normal bone mineral density.

Among participants without CKD progression, osteopenia was present in 5%. In contrast, osteopenia was significantly more prevalent among those who progressed to more advanced CKD stages (24.1% vs. 5.0%; p=0.018) (Table 7). No significant association was observed between CKD progression and osteoporosis or low bone mass for age.

Parameter	CKD progression (n=29)	No progression (n=61)	p
Osteopenia	7 (24.1%)	3 (5.0%)	0.018
Osteoporosis	2 (6.9%)	3 (5.0%)	1.000
Low BMD for age	2 (6.9%)	2 (3.3%)	0.843
Low-impact fractures	1 (3.4%)	2 (3.3%)	1.000

Values as n (%). Pearson chi-square with Yates correction. BMD = bone mineral density. Data available for 90 of 113 participants (DXA available in 104; CKD progression data complete in 90).

Table 7. Bone health and CKD progression in participants with chronic hypoparathyroidism.

Discussion

This multicenter retrospective cohort study characterizes the long-term clinical profile and complications of 113 patients with chronic HP receiving conventional therapy. This is the largest Brazilian cohort on this topic published to date. In this study, participants with chronic HP receiving long-term conventional therapy (median duration 7.5 years) showed improvement in hypocalcemia and hyperphosphatemia. Despite this biochemical improvement, a substantial impact on renal health was observed, with a decline in eGFR and progression of CKD stage in approximately one-third of the cohort. Notably, more advanced CKD stages were strongly associated with the presence of SAH and DM. Furthermore, renal function decline was associated with a higher prevalence of osteopenia.

The demographic and etiological profile of our cohort is consistent with findings from other international series, with a predominance of middle-aged women undergoing cervical surgery [10–12]. The main surgical indication was non-toxic multinodular goiter (63.8%), followed by thyroid cancer (18.1%). In the international literature, these two conditions consistently appear as the main causes of postsurgical HP, although their order of prevalence varies across studies. Zanchetta et al. [13] reported thyroid cancer as the predominant cause (45.6%), whereas Underbjerg et al. [14] and Reinke et al. [11] described a pattern similar to that observed in our cohort, with a predominance of benign disease. These differences may reflect variations in surgical indications across countries, the prevalence of thyroids diseases, differences in gland size, the extent of surgical resection, the frequency of reoperations, and the experience of the surgical team.

Ethnic heterogeneity was observed in our cohort, which comprised 50% White and 50% non-White patients. This finding differs from that reported in a recent study comparing patients with HP in Western and Eastern populations, in which the Western population was predominantly White [15]. This difference likely reflects the extensive ethnic admixture in Brazil, where approximately 43.5% of the population self-identifies as White and the largest proportion (45.3%) identifies as mixed race [16].

The significant increase in BMI during follow-up reflects global trends [17] and has clinical relevance given the association of obesity with CKD, SAH, and DM [18–20]. In a multivariate analysis of 42 European patients with HP and a median disease duration of 11 years, Di Filippo et al. [21] identified obesity as an independent predictor of CKD (OR 3.05; $p = 0.035$). In our cohort, however, no significant association was observed between BMI and CKD progression ($p = 0.178$). This discrepancy may reflect differences in BMI distribution, duration of follow-up, or the influence of potential unadjusted confounders, such as SAH and DM, which in our analysis showed a stronger association with more advanced CKD stages. Further prospective studies are needed to clarify the independent role of obesity in the progression of renal dysfunction in patients with chronic HP.

Conventional therapy in our cohort primarily consisted of elemental calcium supplementation and the use of the active form of vitamin D, calcitriol, consistent with findings previously reported in the literature [22,23]. Treatment strategies vary across different geographic settings, as demonstrated in a French database analysis in which off-label teriparatide prescriptions were more frequent [24], and in a Japanese study where the use of active vitamin D predominated over calcium supplementation [25]. In our cohort, the high proportion of participants receiving calcium supplements may reflect the low dietary calcium intake in the Brazilian population, estimated at less than 500 mg/day [26]. The predominance of calcitriol over other forms of vitamin D likely reflects its availability free of charge to patients with HP through the Brazilian public health system, which may facilitate both access and adherence to treatment

Hypercalciuria, defined as urinary calcium excretion above 4 mg/kg/24h, was documented in 15% of participants at some point during follow-up; at FA, 8.5% still exceeded the recommended thresholds. The lower urinary calcium excretion observed among thiazide users is consistent with the expected pharmacological effect of these medications in reducing calciuria [27].

Interestingly, the high proportion of participants receiving thiazides in our cohort (43.4%) contrasts with findings reported in the literature, where higher prevalences of hypercalciuria are generally observed in settings with lower use of this medication. In a European study including 166 patients with HP, Ridder et al. [28] reported hypercalciuria in 65.7% of participants, whereas only 11.8% were receiving thiazide therapy. Similarly, Meola et al. [29] described hypercalciuria in 54.9% of participants, with only 2% receiving thiazides; these individuals were excluded from the analysis of urinary calcium excretion. Lower prevalences of hypercalciuria have been reported in other studies, including 27.6% in an endocrinology center in Turkey [30], where 7.2% of patients were using thiazides, and 27.2% in a Brazilian study [10], in which the use of diuretics was not described.

Several factors may explain these differences. Beyond individual physiological variability, methodological aspects such as differences in the standardization of 24-hour urine collection and incomplete documentation of urinary calcium measurements in medical records may have contributed to the variability observed. Furthermore, some participants were receiving thiazides for indications unrelated to the control of calciuria, such as SAH alone (17.7%) or other reasons not clearly identified in the medical record review, which may also have influenced the prevalence of hypercalciuria observed.

In the present study, 32.3% of participants receiving conventional therapy for HP experienced worsening of CKD stage. At follow-up, 35.4% had eGFR > 90 mL/min/1.73 m², 47.8% had eGFR between 60 and 90 mL/min/1.73 m², and 16.8% had eGFR below 60 mL/min/1.73 m², similar to findings reported by Underbjerg et al. [14]. The proportion of individuals with HP and CKD stage ≥3 in our cohort exceeds that observed in the Brazilian population. According to a national systematic review [31], only 1.43% of individuals self-reported kidney disease, and in healthcare settings up to 13.63% had documented eGFR below 60 mL/min/1.73 m².

The high prevalence of CKD among individuals with HP is further supported by a meta-analysis published in 2021 [7], in which the proportion of CKD stage ≥3 ranged from 12% to 23% among patients with a mean HP duration between 9 and 15.9 years. Moreover, in one of the included studies, among participants with longer disease duration (17 years), 41% had eGFR below 60 mL/min/1.73 m², suggesting that deterioration of renal function is strongly influenced by the duration of HP.

In addition, Luk et al. [32], in a population-based study, identified permanent HP as an independent risk factor for sustained reduction in eGFR. In a retrospective analysis conducted by Spanish investigators [33], other factors were also found to be significantly associated with deterioration of renal function in patients with HP, including SAH, DM, dyslipidemia, and nephrolithiasis. Consistent with these findings, SAH, dyslipidemia, and DM were among the most prevalent comorbidities in our cohort, and a higher prevalence of SAH and DM was observed in participants with more advanced CKD stages.

The prevalence of nephrolithiasis in patients with HP receiving conventional therapy varies considerably. In a meta-analysis including 13 studies, of which 6 reported data on this condition, nephrolithiasis rates ranged from 0% to 35.5%, with lower rates observed in studies with shorter disease duration [7]. A systematic review [34] reported a median nephrolithiasis prevalence of 15% across studies, nearly twice that observed in our cohort (8.8%). The relatively small number of participants with nephrolithiasis in our cohort may have limited the statistical power to detect significant associations between this complication and other variables, including renal outcomes and pharmacological treatment.

Less frequent comorbidities and complications in our cohort included cataract, CVD, and BGC, whose prevalence varies widely in the literature [12,34,35]. Many of these conditions require active investigation through complementary examinations, which may contribute to underdiagnosis in routine clinical practice. In a study analyzing patterns of medical practice, for example, only 23% of professionals reported screening for ocular complications and 4% for BGC [24]. In addition, it is important to highlight the absence of recent national protocols establishing the optimal timing for systematic screening of these complications in patients with HP, which may hinder their early recognition and management. By contrast, the most recent international recommendations suggest that additional investigations should be guided predominantly by the presence of signs or symptoms [5].

It is well established that PTH exerts a direct influence on bone remodeling, and that its deficiency or chronic absence in patients with HP reduces bone turnover, resulting in increased bone mineral density [36]. Sakane et al. [37] observed that most individuals with HP had DXA results within the normal range, whereas 32.4% had osteopenia and 2.9% had osteoporosis. In addition, they reported that patients with postsurgical HP who were postmenopausal, had DM, higher BMI, or older age showed impaired bone quality assessed by the trabecular bone score. In our cohort, we observed a higher prevalence of osteopenia among participants who

experienced CKD stage progression compared with those without progression, supporting the hypothesis that osteopenia in this subgroup is more likely attributable to the mineral and hormonal metabolism disturbances associated with CKD than to HP alone.

Evidence regarding fracture risk in patients with HP remains limited. In a meta-analysis conducted by Pal et al. [38], which included seven observational studies, an increased risk of vertebral fractures was observed in individuals with non-surgical HP, but not in those with postsurgical HP (OR 2.31; $p = 0.003$). In contrast, Ahn et al. [39], in a Korean population-based cohort, demonstrated that the risk of any fracture was significantly lower in participants with postsurgical HP compared with individuals without HP ($p = 0.037$). Consistent with these findings, the occurrence of fragility fractures in our cohort was low (2.8%). Studies with longer disease duration are needed to better characterize the long-term skeletal consequences of chronic HP, particularly in patients with postsurgical HP.

This study has limitations inherent to its retrospective observational design, including the inability to establish causal relationships, and the absence of a control group for direct comparison of the findings. On the other hand, several strengths should be highlighted, including the inclusion of data from four Endocrinology Reference Centers, constituting the largest Brazilian cohort of individuals with chronic HP to our knowledge. Furthermore, the longitudinal design allowed a comprehensive evaluation of clinical, biochemical, and complication-related parameters, encompassing multiple variables potentially influenced by conventional therapy.

Conclusion

Although conventional therapy achieves adequate metabolic control in patients with chronic hypoparathyroidism—with improvement in serum calcium and phosphate—relevant renal complications persist over long-term follow-up, particularly eGFR decline and CKD progression. Advanced CKD stages were strongly associated with SAH and DM. The high prevalence of these comorbidities reinforces the need for rigorous and systematic monitoring of renal function and cardiometabolic risk factors in this population. Prospective studies are warranted to define preventive strategies that may mitigate renal disease progression.

Statements and Declarations

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

Competing Interests
The authors declare that they have no conflict of interest.

Author Contributions
Henri and Debora contributed to study conception and design, data collection, data analysis, and manuscript drafting. All authors contributed to data interpretation, critically revised the manuscript, and approved the final version.

Ethics Approval
The study was approved by the Research Ethics Committees of all participating institutions (HUAP-UFF, HFSE, HUPE-UERJ, and IEDE; CAAE numbers: 82845317.0.0000.5243, 82845317.0.3001.5252, 82845317.0.3002.5259, and 82845317.0.3003.5266). The study was conducted in accordance with the Declaration of Helsinki.

Consent to Participate
Written informed consent was obtained from all individual participants included in the study.

Data Availability
The datasets generated and/or analysed during the current study are not publicly available due to ethical and privacy restrictions but are available from the corresponding author on reasonable request.

References

1. Khan S, Khan AA. Hypoparathyroidism: diagnosis, management and emerging therapies. Nat Rev Endocrinol. 2025;21(6):360-374. https://doi.org/10.1038/s41574-024-01075-8

2. Mannstadt M, et al. Hypoparathyroidism. Nat Rev Dis Primers. 2017;3:17055. https://doi.org/10.1038/nrdp.2017.55

3. Bilezikian JP. Hypoparathyroidism. J Clin Endocrinol Metab. 2020;105(6):1722-1736. https://doi.org/10.1210/clinem/dgaa113

4. Cetani F, et al. Unveiling the complexities of hypoparathyroidism: a comprehensive review of clinical manifestations, diagnosis, and novel therapies. J Endocrinol Invest. 2025. https://doi.org/10.1007/s40618-025-02760-9

5. Bollerslev J, et al. Revised European Society of Endocrinology clinical practice guideline: treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2025;193(5):G49-G78. https://doi.org/10.1093/ejendo/lvaf222

6. De Alencar JM, et al. Clinical profile and quality of life scores in chronic hypoparathyroidism: a transversal retrospective study. Braz J Health Rev. 2023;6(2):6018-6033. https://doi.org/10.34119/bjhrv6n2-125

7. Gosmanova EO, et al. Renal complications in patients with chronic hypoparathyroidism on conventional therapy: a systematic literature review. Rev Endocr Metab Disord. 2021;22(2):297-316. https://doi.org/10.1007/s11154-020-09613-1

8. Inker LA, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737-1749. https://doi.org/10.1056/NEJMoa2102953

9. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(4 Suppl):S117-S314. https://doi.org/10.1016/j.kint.2023.10.018

10. Lopes MP, et al. Hypoparathyroidism and pseudohypoparathyroidism: etiology, laboratory features and complications. Arch Endocrinol Metab. 2016;60(6):532-536. https://doi.org/10.1590/2359-3997000000221

11. Reinke R, et al. Increased risk of chronic kidney disease after total thyroidectomy: a nationwide matched cohort study. J Clin Endocrinol Metab. 2025;110(5):e1466-e1472. https://doi.org/10.1210/clinem/dgae534

12. Díez JJ, et al. Incident comorbidities in patients with chronic hypoparathyroidism after thyroidectomy: a multicenter nationwide study. Front Endocrinol (Lausanne). 2024;15:1348971. https://doi.org/10.3389/fendo.2024.1348971

13. Zanchetta MB, et al. Hipopara-Red, real life experience in 322 patients with hypoparathyroidism. J Endocr Soc. 2020;5(2):bvaa181. https://doi.org/10.1210/jendso/bvaa181

14. Underbjerg L, Sikjaer T, Rejnmark L. Long-term complications in patients with hypoparathyroidism evaluated by biochemical findings: a case-control study. J Bone Miner Res. 2018;33(5):822-831. https://doi.org/10.1002/jbmr.3368

15. Yang YY, et al. Hypoparathyroidism: similarities and differences between Western and Eastern countries. Osteoporos Int. 2025;36(3):391-402. https://doi.org/10.1007/s00198-024-07352-6

16. Instituto Brasileiro de Geografia e Estatística. Censo demográfico 2022 [Internet]. Rio de Janeiro: IBGE; 2023 [cited 2025 Nov 1]. Available from: https://censo2022.ibge.gov.br

17. World Obesity Federation. World Obesity Atlas 2025 [Internet]. London: World Obesity Federation; 2025 [cited 2025 Oct 26]. Available from: https://data.worldobesity.org

18. Bombelli M, et al. Impact of body mass index and waist circumference on the long-term risk of diabetes mellitus, hypertension, and cardiac organ damage. Hypertension. 2011;58(6):1029-1035. https://doi.org/10.1161/HYPERTENSIONAHA.111.175125

19. Ying J, et al. Global, regional, and national burdens of chronic kidney disease attributable to high body mass index from 1990 to 2021. Front Public Health. 2025;13:1612300. https://doi.org/10.3389/fpubh.2025.1612300

20. Fuss CT, et al. Cardiovascular status in chronic hypoparathyroidism: a systematic cross-sectional assessment in 168 patients. Eur J Endocrinol. 2025;192(4):373-384. https://doi.org/10.1093/ejendo/lvaf023

21. Di Filippo L, et al. Obesity and blunted FGF23 response associate with kidney impairment in patients with hypoparathyroidism. Endocrine. 2025;89(1):250-258. https://doi.org/10.1007/s12020-025-04221-y

22. Mitchell DM, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 2012;97(12):4507-4514. https://doi.org/10.1210/jc.2012-1808

23. Gittoes N, et al. The PARADIGHM registry for patients with chronic hypoparathyroidism: study protocol and interim baseline patient characteristics. BMC Endocr Disord. 2021;21(1):232. https://doi.org/10.1186/s12902-021-00888-2

24. Bertocchio JP, et al. Practice patterns for chronic hypoparathyroidism: data from patients and physicians in France. Endocr Connect. 2022;11(1):e210350. https://doi.org/10.1530/EC-21-0350

25. Hasegawa M, et al. Prevalence and characteristics of postoperative and nonoperative chronic hypoparathyroidism in Japan. JBMR Plus. 2024;8(9):ziae100. https://doi.org/10.1093/jbmrpl/ziae100

26. Instituto Brasileiro de Geografia e Estatística. Pesquisa de orçamentos familiares 2017-2018: análise do consumo alimentar pessoal no Brasil [Internet]. Rio de Janeiro: IBGE; 2020 [cited 2025 Nov 2]. Available from: https://biblioteca.ibge.gov.br

27. Escribano J, et al. Pharmacological interventions for preventing complications in idiopathic hypercalciuria. Cochrane Database Syst Rev. 2009;(1):CD004754. https://doi.org/10.1002/14651858.CD004754.pub2

28. Ridder LO, et al. Determinants of hypercalciuria and renal calcifications in chronic hypoparathyroidism: a cross-sectional study. Clin Endocrinol (Oxf). 2021;95(2):286-294. https://doi.org/10.1111/cen.14470

29. Meola A, et al. Efficacy and safety of long-term management of patients with chronic post-surgical hypoparathyroidism. J Endocrinol Invest. 2018;41(10):1221-1226. https://doi.org/10.1007/s40618-018-0857-5

30. Turan Erdogan B, et al. Evaluation of compliance with international guidelines during the follow-up of hypoparathyroidism. Int J Endocrinol. 2025;2025:3174295. https://doi.org/10.1155/ije/3174295

31. Marinho AWGB, et al. Prevalência de doença renal crônica em adultos no Brasil: revisão sistemática da literatura. Cad Saude Colet. 2017;25(3):379-388. https://doi.org/10.1590/1414-462X201700030134

32. Luk Y, et al. Long-term kidney outcomes in patients with permanent hypoparathyroidism after total thyroidectomy. Surgery. 2024;176(3):700-707. https://doi.org/10.1016/j.surg.2024.05.005

33. López-Mezquita Torres E, et al. Factors related to decline of renal function in patients with chronic hypoparathyroidism. J Clin Med. 2025;14(16):5732. https://doi.org/10.3390/jcm14165732

34. Yao L, et al. Complications, symptoms, presurgical predictors in patients with chronic hypoparathyroidism: a systematic review. J Bone Miner Res. 2022;37(12):2642-2653. https://doi.org/10.1002/jbmr.4673

35. Cherchir F, et al. Long-term complications of permanent hypoparathyroidism in adults: prevalence and associated factors. Endocrine. 2024;84(3):1164-1171. https://doi.org/10.1007/s12020-024-03765-9

36. Carvalho ARTB, et al. Predictors of lumbar spine trabecular bone score in women with postsurgical hypoparathyroidism. Bone. 2025;190:117274. https://doi.org/10.1016/j.bone.2024.117274

37. Sakane EN, et al. Predictors of poor bone microarchitecture assessed by trabecular bone score in postsurgical hypoparathyroidism. J Clin Endocrinol Metab. 2019;104(12):5795-5803. https://doi.org/10.1210/jc.2019-00698

38. Pal R, et al. Fracture risk in hypoparathyroidism: a systematic review and meta-analysis. Osteoporos Int. 2021;32(11):2145-2153. https://doi.org/10.1007/s00198-021-05966-8

39. Ahn SH, et al. Risk of fractures in thyroid cancer patients with postoperative hypoparathyroidism: a nationwide cohort study in Korea. J Bone Miner Res. 2023;38(9):1268-1277. https://doi.org/10.1002/jbmr.4871