



Risk of Chronic Kidney Disease and Estimated Glomerular Filtration Rate Decline in Patients with Chronic Hypoparathyroidism: A Retrospective Cohort Study

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ABSTRACT

Introduction: Chronic hypoparathyroidism, treated with conventional therapy of oral calcium supplements and active vitamin D, may increase the risk of kidney complications. This study examined risks of development and progression of chronic kidney disease (CKD) and estimated glomerular filtration rate (eGFR)

decline in patients with chronic hypoparathyroidism.

Methods: A retrospective cohort study using a managed care claims database in the United States from January 2007 to June 2017 included patients with chronic hypoparathyroidism (excluding those receiving parathyroid hormone) and randomly selected patients without hypoparathyroidism followed for up to 5 years. Main outcome measures were (1) development of CKD, defined as new diagnosis of CKD stage 3 and higher or ≥ 2 eGFR measurements < 60 ml/min/1.73 m² ≥ 3 months apart, (2) progression of CKD, defined as increase in baseline CKD stage, (3) progression to end-stage kidney disease (ESKD), and (4) eGFR decline $\geq 30\%$ from baseline. Time-to-event analyses included Kaplan-Meier analyses with log-rank tests, and both unadjusted and adjusted Cox proportional hazards models were used to compare outcomes between cohorts.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12325-021-01658-1>.

Results: The study included 8097 adults with and 40,485 without chronic hypoparathyroidism. In Kaplan-Meier analyses, patients with chronic hypoparathyroidism had higher risk of developing CKD and CKD progression and higher rates of eGFR decline (all $P < 0.001$). In multivariable Cox models adjusted for baseline characteristics, hazard ratios (95% confidence intervals [CIs]) were 2.91 (2.61–3.25) for developing CKD, 1.58 (1.23–2.01) for CKD stage progression, 2.14 (1.51–3.04) for progression to ESKD, and 2.56 (1.62–4.03) for eGFR decline

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(all $P < 0.001$) among patients with chronic hypoparathyroidism compared with those without hypoparathyroidism.

Conclusion: Patients with chronic hypoparathyroidism have increased risk of development and progression of CKD and eGFR decline compared with those without hypoparathyroidism. Further studies are warranted to understand underlying mechanisms for the associations between chronic hypoparathyroidism and kidney disease.

Keywords: Active vitamin D; Calcium; Chronic hypoparathyroidism; Chronic kidney disease; End-stage kidney disease

Key Summary Points

Why carry out this study?

Chronic hypoparathyroidism is a rare disorder characterized by absent or inappropriately low levels of parathyroid hormone that is associated with abnormal mineral homeostasis.

Studies conducted in small cohorts have demonstrated that chronic hypoparathyroidism is associated with an increased risk of renal complications; larger studies are needed to confirm these findings.

This retrospective cohort study of 8097 patients with chronic hypoparathyroidism examined risks of development and progression of chronic kidney disease (CKD) and estimated glomerular filtration rate (eGFR) decline.

What was learned from the study?

Patients with chronic hypoparathyroidism had a higher risk of developing CKD and CKD progression and higher rates of decline in eGFR compared with those without hypoparathyroidism.

Further studies are necessary to understand underlying mechanisms for the associations between kidney disease and chronic hypoparathyroidism.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13713463>.

INTRODUCTION

Chronic hypoparathyroidism is a rare endocrine disorder characterized by hypocalcemia, hyperphosphatemia, and absent or insufficient parathyroid hormone (PTH) production [1, 2]. Hypoparathyroidism is most commonly caused by damage to or removal of the parathyroid glands during thyroid surgery but can also be of autoimmune or genetic origin [1, 2]. In the absence of PTH, the mechanisms regulating calcium transport and phosphate reabsorption in the PTH receptor-rich renal tubule are deregulated resulting in disruption to the major role of the kidney in controlling calcium and phosphate homeostasis [3].

Previous studies have found increased risk of renal complications in patients with chronic hypoparathyroidism managed with conventional therapy consisting of oral calcium and active vitamin D [4, 5]. Recent studies have added to the body of evidence regarding renal complications in patients with chronic hypoparathyroidism [6–10]. A Scottish study identified a significantly higher risk of renal failure, defined as estimated glomerular filtration rate (eGFR) < 30 ml/min, in patients with hypoparathyroidism compared with age- and gender-matched controls [6]. In a cross-sectional Belgian study, kidney stones and/or nephrocalcinosis was present in 22% of patients on conventional therapy with available renal imaging from the prior 10 years; history of kidney stones did not differ between surgical and nonsurgical etiologies [7]. Two Danish retrospective cohort studies found that nonsurgical hypoparathyroidism and postsurgical hypoparathyroidism were associated with increased risk of renal stones, renal insufficiency, and renal diseases, defined using

diagnosis codes [5, 8]. Patients with long-standing hypoparathyroidism treated with conventional therapy require close monitoring of symptoms of hypoparathyroidism and comorbidities, including development of chronic kidney disease (CKD), risk of renal stones, and renal calcifications [2, 7, 9, 10]. Previous studies were limited by the small sample size and evaluated a limited range of kidney outcomes. Therefore, we conducted a large-scale retrospective study aiming to more comprehensively examine risks of development and progression of CKD and decline in eGFR in patients with chronic hypoparathyroidism.

METHODS

Data Source and Study Design

This retrospective study used data from a large managed care claims database in the United States. The database covers both commercial (employer database) and Medicare Advantage beneficiaries and reflects ≥ 14 million members per year from the first quarter of 2007 to the second quarter of 2017. As this study used de-identified licensed data from a Health Insurance Portability and Accountability Act-compliant managed care database, ethics committee approval and informed consent were not required.

Patients from the database were divided into two cohorts: those with chronic hypoparathyroidism and those without chronic hypoparathyroidism. Diagnosis of hypoparathyroidism was confirmed with at least two medical claims at least 6 months apart. All eligible patients were ≥ 18 years of age, had not been treated with recombinant parathyroid hormone therapies, and were required to have at least 6 months of continuous eligibility before the index date. The index date was defined as the first date of a diagnosis of hypoparathyroidism at least 6 months after initial diagnosis for the cohort of patients with hypoparathyroidism and the date of an eligible, randomly selected claim for the cohort of patients without hypoparathyroidism. In both cohorts, the baseline period was defined as the 6 months of

continuous eligibility before the index date. Patients were followed for up to 5 years or until the end of continuous eligibility (i.e., uninterrupted coverage by insurance provider), whichever occurred first. Figure 1 illustrates the selection criteria used to obtain the study population.

Outcome Measures

Outcomes of interest included risk of development of incident CKD, progression of CKD, and decline in eGFR. For the incident CKD analysis, patients without baseline CKD were included. Baseline CKD was defined as (1) incident CKD stages 3–5 (or CKD unspecified) identified by International Statistical Classification of Diseases and Related Health Problems, 9th (ICD-9) or 10th (ICD-10) Revision, Clinical Modification diagnosis codes (Supplementary Table 1) or (2) one eGFR value < 60 ml/min/1.73 m². eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [11]. Among patients free of baseline CKD, time to incident CKD was defined as time to the first date of either (1) a diagnosis code for CKD stages 3–5 or (2) ≥ 2 eGFR values < 60 ml/min/1.73 m² at least 3 months apart.

Chronic kidney disease progression was assessed among patients with baseline CKD stage 3 or 4 (i.e., patients with a diagnosis code for stage 3 or 4 or eGFR of 30–59 ml/min/1.73 m² [stage 3] or 15–29 ml/min/1.73 m² [stage 4]). CKD progression to a higher stage was defined as the time to first evidence of (1) a diagnosis code for a higher CKD stage or (2) ≥ 2 eGFR values at least 3 months apart, both representing a higher CKD stage. Progression to end-stage kidney disease (ESKD), assessed among patients with baseline CKD stage 3 or 4, was defined as the time to first evidence of ESKD indicated by either (1) a diagnosis code for CKD stage 5 or (2) ≥ 2 eGFR measurements < 15 ml/min/1.73 m² at least 3 months apart (Table 1). Outcome dates for CKD progression and progression to ESKD were identified by the date of the first eGFR measurement.

Time to first decline in eGFR was assessed among patients with ≥ 1 eGFR measurement

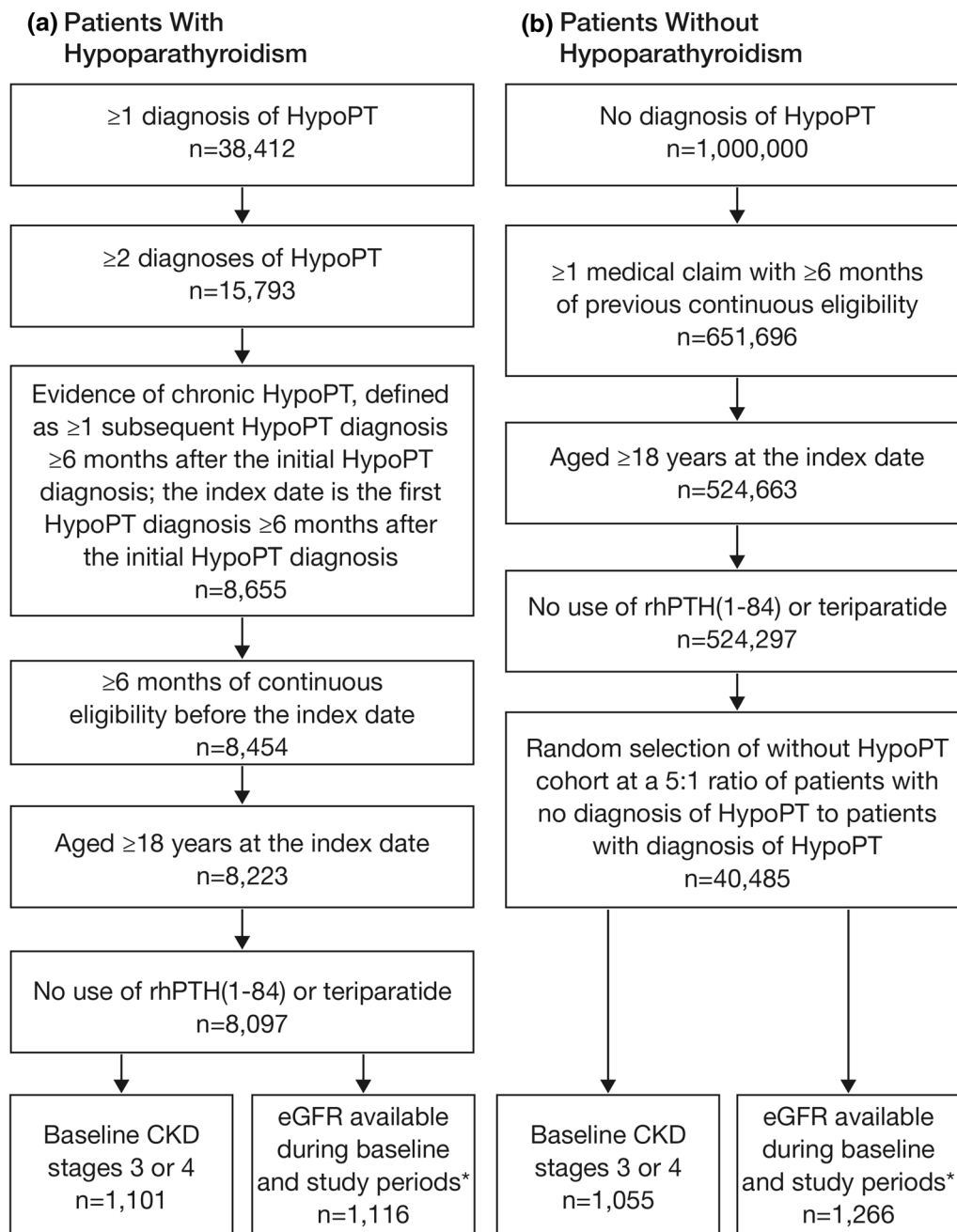


Fig. 1 Sample selection of patients **a** with and **b** without chronic hypoparathyroidism. *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *HypoPT* hypoparathyroidism, *rhPTH(1-84)* recombinant human parathyroid hormone (1-84). *Patients were required to have ≥ 1 eGFR measurement during the baseline period and ≥ 2 eGFR measurements at least 3 months apart

during the study period. The index date of the study period was the first date of a diagnosis of hypoparathyroidism at least 6 months after initial diagnosis for the cohort of patients with hypoparathyroidism and the date of an eligible, randomly selected claim for the cohort of patients without hypoparathyroidism. In both cohorts, the baseline period was defined as the 6 months before the index date

Table 1 Demographics and baseline characteristics during the 6 months before the index date among patients with or without a diagnosis of hypoparathyroidism

Characteristic	Patient cohorts					
	Overall		Baseline CKD stage 3 or 4		eGFR analysis	
	HypoPT (<i>n</i> = 8097)	Without HypoPT (<i>n</i> = 40,485)	HypoPT (<i>n</i> = 1101)	Without HypoPT (<i>n</i> = 1055)	HypoPT (<i>n</i> = 1116)	Without HypoPT (<i>n</i> = 1266)
Age, mean ± SD, years	59 ± 16.3 ^a	47 ± 18.0	71 ± 11.6 ^a	72 ± 10.9	61 ± 15.2 ^a	61 ± 14.7
Female sex, <i>n</i> (%)	6173 (76.2) ^a	22,043 (54.4)	739 (67.1) ^a	577 (54.7)	840 (75.3) ^a	705 (55.7)
Race/ethnicity, <i>n</i> (%)						
White	5242 (64.7) ^a	25,560 (63.1)	740 (67.2)	700 (66.4)	790 (70.8)	879 (69.4)
Black/African American	711 (8.8)	3458 (8.5)	90 (8.2)	112 (10.6)	101 (9.1)	137 (10.8)
Hispanic/Latino	833 (10.3)	3951 (9.8)	122 (11.1)	107 (10.1)	184 (16.5)	179 (14.1)
Asian/Pacific Islander	239 (3.0) ^a	1555 (3.8)	21 (1.9)	23 (2.2)	41 (3.7) ^a	71 (5.6)
Unknown	1072 (13.2) ^a	5961 (14.7)	128 (11.6)	113 (10.7)	0 (0.0)	0 (0.0)
CKD, defined by diagnosis codes and eGFR values, <i>n</i> (%)						
Stage 3	885 (10.9) ^a	915 (2.3)	885 (80.4) ^a	915 (86.7)	326 (29.2)	235 (18.6)
Stage 4	216 (2.7) ^a	140 (0.3)	216 (19.6) ^a	140 (13.3)	67 (6.0)	28 (2.2)
ESKD ^{†b}	223 (2.8) ^a	154 (0.4)	0	0	28 (2.5)	10 (0.8)
eGFR, ml/min/1.73 m ² , median (IQR)	–	–	–	–	72.3 (53.6–90.6) ^a	82.2 (65.3–95.5)
Comorbidities, <i>n</i> (%)						
Heart failure	481 (5.9) ^a	967 (2.4)	161 (14.6) ^a	209 (19.8)	72 (6.5)	70 (5.5)
Hypertension	3535 (43.7) ^a	10,216 (25.2)	816 (74.1) ^a	862 (81.7)	608 (54.5) ^a	773 (61.1)
Kidney or genitourinary infection	874 (10.8) ^a	2373 (5.9)	199 (18.1)	191 (18.1)	142 (12.7) ^a	119 (9.4)
Type 1 diabetes	230 (2.8) ^a	453 (1.1)	62 (5.6)	57 (5.4)	47 (4.2)	40 (3.2)
Type 2 diabetes	1670 (20.6) ^a	4378 (10.8)	412 (37.4) ^a	474 (44.9)	283 (25.4) ^a	389 (30.7)
Medications, <i>n</i> (%)						
Use of NSAIDs, PPIs, and cimetidine	2097 (25.9) ^a	6949 (17.2)	360 (32.7)	315 (29.9)	332 (29.7)	357 (28.2)
Use of ≥ 1 drug from the following classes: ACE inhibitors, ARBs, and diuretics	1902 (23.5) ^a	5568 (13.8)	437 (39.7) ^a	472 (44.7)	315 (28.2)	402 (31.8)

Table 1 continued

Characteristic	Patient cohorts					
	Overall		Baseline CKD stage 3 or 4		eGFR analysis	
	HypoPT (<i>n</i> = 8097)	Without HypoPT (<i>n</i> = 40,485)	HypoPT (<i>n</i> = 1101)	Without HypoPT (<i>n</i> = 1055)	HypoPT (<i>n</i> = 1116)	Without HypoPT (<i>n</i> = 1266)
Use of oral thiazide diuretics	1388 (17.1) ^a	4017 (9.9)	237 (21.5)	258 (24.5)	226 (20.3)	291 (23.0)

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *HypoPT* hypoparathyroidism, *IQR* interquartile range, *NSAID* nonsteroidal anti-inflammatory drug, *PPI* proton pump inhibitor, *SD* standard deviation

^a *P* < 0.05 between cohorts

^b Defined among patients with baseline CKD stages 3–4 with a diagnosis code for CKD stage 5 or ≥ 2 eGFR measurements < 15 ml/min/1.73 m² at least 3 months apart both representing a higher CKD stage

during baseline and ≥ 2 eGFR measurements at least 3 months apart during the study period. The decline in eGFR outcome was reached when ≥ 2 eGFR measurements at least 3 months apart during the study period both showed a $\geq 30\%$ decline from baseline [12], with the outcome date identified as the earliest of these eGFR measurements.

Statistical Analysis

Descriptive statistics (mean, standard deviation, percentage) were used to describe and compare demographics and clinical characteristics for patients with and without chronic hypoparathyroidism. Comparisons between cohorts were made using Wilcoxon rank-sum tests for continuous variables and chi-square tests for dichotomous variables.

Time-to-event analyses included Kaplan-Meier analyses with log-rank tests and both unadjusted and adjusted Cox proportional hazards models to compare risks of development and progression of CKD and eGFR decline between cohorts. The multivariable Cox models were adjusted for demographic characteristics (age, sex, race, region, and index year) and clinical characteristics (heart failure, hypertension, diabetes, and medication use). CKD progression analyses also adjusted for baseline CKD

stage, and eGFR analyses also adjusted for baseline eGFR value. Sensitivity analyses were conducted for the development of CKD and CKD progression using only diagnosis codes for outcome definitions. In addition, for the decline in eGFR outcome, subgroup analyses were performed among patients with baseline eGFR < 60 and ≥ 60 ml/min/1.73 m².

RESULTS

Study Population and Baseline Characteristics

Following sample selection, 8097 patients with chronic hypoparathyroidism and 40,485 patients without hypoparathyroidism were included in the overall study population (Fig. 1). Of these patients, 1101 with chronic hypoparathyroidism and 1055 without hypoparathyroidism had baseline CKD stage 3 or 4 and were included in the CKD progression analysis. Additionally, there were 1116 patients with hypoparathyroidism and 1266 patients without hypoparathyroidism included in the eGFR analysis. Baseline characteristics for the overall study population, the cohort of patients with baseline CKD stage 3 or 4, and the eGFR cohort are shown in Table 1. In the overall

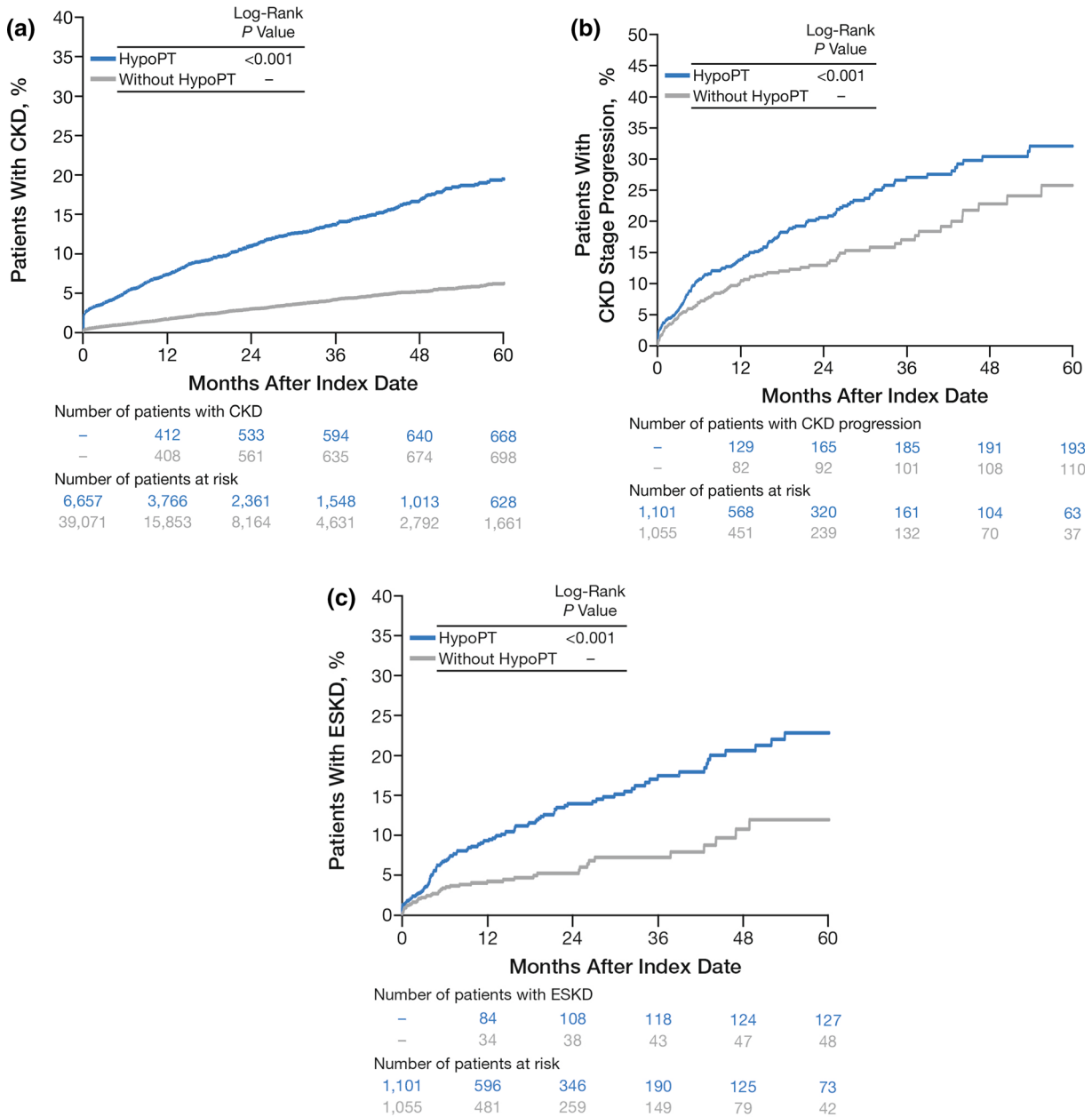


Fig. 2 Time to first instance of **a** CKD stages 3–5^a, **b** CKD stage progression^b, and **c** progression to ESKD^c. *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *HypoPT* hypoparathyroidism. ^aDefined as the first instance of CKD stages 3–5 defined by diagnosis codes and by ≥ 2 eGFR measurements < 60 ml/min/1.73 m² at least 3 months apart on or after the index date among patients without CKD stage 3 or 4, ESKD, or unspecified CKD during the baseline period. ^bDefined as CKD stage progression in

those with CKD stages 3 and 4 at baseline to a higher CKD stage, as indicated by either a diagnosis code for a higher CKD stage or ≥ 2 eGFR measurements at least 3 months apart both representing a higher CKD stage. ^cDefined as the first instance of ESKD by either a diagnosis code for CKD stage 5 or ≥ 2 eGFR measurements < 15 ml/min/1.73 m² at least 3 months apart on or after the index date among patients with CKD stage 3 or 4 during the baseline period

Table 2 Risk of development and progression of CKD in patients with chronic hypoparathyroidism compared with those without hypoparathyroidism

Outcome, estimated effect of hypoparathyroidism	HR	95% CI	P value
Incident CKD ^a			
Unadjusted	4.23	3.80–4.71	< 0.001
Adjusted ^b	2.91	2.61–3.25	< 0.001
CKD stage progression ^a			
Unadjusted	1.49	1.18–1.89	< 0.001
Adjusted ^{b,c}	1.58	1.23–2.01	< 0.001
CKD progression to ESKD ^a			
Unadjusted	2.23	1.60–3.10	< 0.001
Adjusted ^{b,c}	2.14	1.51–3.04	< 0.001

CI confidence interval, CKD chronic kidney disease, ESKD end-stage kidney disease, HR hazard ratio

^a Patients without hypoparathyroidism served as the reference group for all analyses

^b Multivariable Cox models adjusted for demographic (age, sex, race, region, and index year) and clinical (heart failure, hypertension, diabetes, and medication use) characteristics at baseline

^c CKD stage progression and progression to ESKD models also adjusted for baseline CKD stage

study population, patients with chronic hypoparathyroidism were older and a greater proportion were women compared with patients who did not have hypoparathyroidism (both $P < 0.001$). At baseline, a higher proportion of patients with chronic hypoparathyroidism had CKD stages 3–5, heart failure, hypertension, and diabetes compared with those without hypoparathyroidism (all $P < 0.001$).

Risk of Development and Progression of Chronic Kidney Disease

Compared with patients who did not have hypoparathyroidism, Kaplan-Meier analyses showed that patients with chronic hypoparathyroidism had a significantly increased risk of developing incident CKD stage 3 and higher

(log-rank $P < 0.001$; Fig. 2a). Patients with chronic hypoparathyroidism also had a significantly increased risk of progression to a higher CKD stage (log-rank $P < 0.001$; Fig. 2b) and progression to ESKD compared with patients without hypoparathyroidism (log-rank $P < 0.001$; Fig. 2c). Similar to unadjusted analyses, in multivariable analyses adjusted for baseline characteristics, patients with chronic hypoparathyroidism were at higher risk for the development of incident CKD (adjusted hazard ratio [HR], 2.91; 95% confidence interval [CI] 2.61–3.25) compared with patients who did not have hypoparathyroidism. Additionally, patients with chronic hypoparathyroidism and CKD at baseline had increased risk of progression to a higher CKD stage and ESKD; adjusted HRs were 1.58 (95% CI 1.23–2.01) and 2.14 (95% CI 1.51–3.04), respectively, compared with patients without hypoparathyroidism (all $P < 0.001$; Table 2).

A sensitivity analysis was conducted whereby only diagnosis codes were used to define the development of CKD and CKD progression. Similar to the primary analyses, patients with chronic hypoparathyroidism had an increased risk of incident CKD (adjusted HR, 2.84; 95% CI 2.53–3.18) and CKD progression (adjusted HR, 1.58; 95% CI 1.21–2.07) compared with patients without hypoparathyroidism.

Risk of Decline in Estimated Glomerular Filtration Rate

Kaplan-Meier analyses showed that patients with chronic hypoparathyroidism had increased risk of decline in eGFR $\geq 30\%$ from baseline compared with patients who did not have hypoparathyroidism (log-rank $P < 0.001$; Fig. 3). In the adjusted analysis, patients with chronic hypoparathyroidism had an increased risk of decline in eGFR $\geq 30\%$ from baseline (adjusted HR, 2.56; 95% CI 1.62–4.03) compared with the cohort of patients without hypoparathyroidism (Table 3). Similar increased risks of eGFR decline were observed in the sensitivity analyses restricted to patients with baseline eGFR < 60 and ≥ 60 ml/min/1.73 m² (Table 3; Fig. 4a, b).

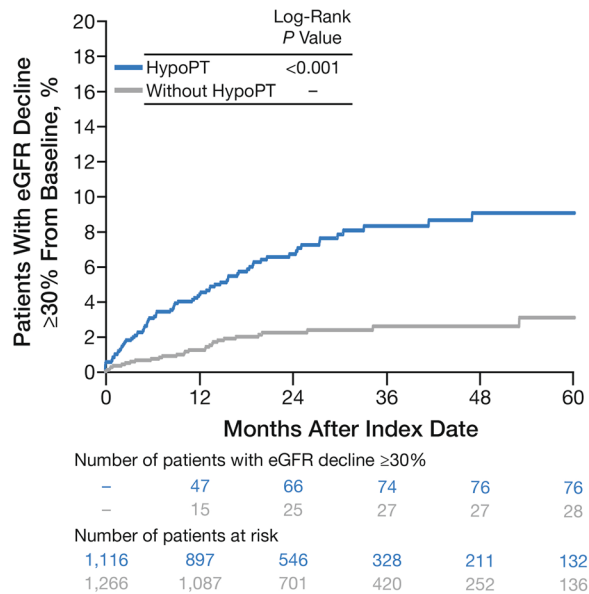


Fig. 3 Time to first eGFR decline $\geq 30\%$ from baseline for all patients. *eGFR* estimated glomerular filtration rate, *HypoPT* hypoparathyroidism

DISCUSSION

The current study demonstrated that patients with chronic hypoparathyroidism were at greater risk of incident CKD, CKD stage progression, progression to ESKD, and faster decline in eGFR compared with patients without hypoparathyroidism during the 5-year follow-up period. These results remained consistent after adjusting for a variety of potential outcome-relevant confounders.

Whereas previous research generally examined smaller cohorts with limited kidney outcomes, this study confirms and expands on the adverse associations between chronic hypoparathyroidism and renal complications in a large-scale cohort of nationally representative patients in the United States using both diagnostic codes and repeat eGFR values. For example, two Danish retrospective studies found that nonsurgical hypoparathyroidism ($N = 180$) and postsurgical hypoparathyroidism ($N = 688$) were associated with increased risk of any renal disease and renal insufficiency defined by diagnostic codes compared with age- and sex-matched controls [5, 8]. Another study from the UK ($N = 280$) identified a significantly

Table 3 Risk of eGFR decline $\geq 30\%$ from baseline in patients with chronic hypoparathyroidism compared with those without hypoparathyroidism*

Population, estimated effect of hypoparathyroidism	HR	95% CI	P value
All patients with available eGFR ^a			
Unadjusted	3.26	2.11–5.02	< 0.001
Adjusted ^b	2.56	1.62–4.03	< 0.001
Patients with eGFR < 60 ml/min/1.73 m ^{2a}			
Unadjusted	2.67	1.38–5.18	0.004
Adjusted ^b	2.11	1.06–4.19	0.033
Patients with eGFR ≥ 60 ml/min/1.73 m ^{2a}			
Unadjusted	2.79	1.55–5.00	< 0.001
Adjusted ^b	3.07	1.67–5.64	< 0.001

CI confidence interval, *eGFR* estimated glomerular filtration rate, *HR* hazard ratio

^a Patients without hypoparathyroidism served as the reference group for all analyses

^b Multivariable Cox models adjusted for demographic (age, sex, race, region, and index year) and clinical (eGFR, heart failure, hypertension, diabetes, and outcome-relevant medication use) characteristics at baseline

higher risk of mortality and renal failure (defined as eGFR < 30 ml/min) in patients with hypoparathyroidism compared with age- and gender-matched control patients [6]. Similarly, a long-term Massachusetts-based registry study of 120 patients with chronic hypoparathyroidism, most of whom were treated with conventional therapy (two patients also received teriparatide), reported a greater proportion of patients with hypoparathyroidism with eGFR < 60 ml/min/1.73 m² compared with age-adjusted norms [4].

Although a growing body of research supports an increased risk of renal complications in patients with chronic hypoparathyroidism [4–6, 8], the underlying mechanism of this risk in the pathophysiology of hypoparathyroidism remains unknown. Chronic hypoparathyroidism is commonly managed with conventional therapy, which is aimed at maintaining a

serum calcium concentration in the lower part of the normal range (i.e., 8.0–8.5 mg/dl) [2, 13–15]. Conventional therapy corrects hypocalcemia by increasing intestinal calcium absorption but does not replace the actions of parathyroid hormone on the kidney that stimulate renal calcium reabsorption and urinary phosphate excretion [15, 16]. Parathyroid hormone exerts calcium-sparing and phosphaturic effects on the kidney, and hormone loss leads to abnormal mineral homeostasis, resulting in unstable serum calcium levels, hyperphosphatemia, and hypercalciuria [15]. In a Danish study of patients with hypoparathyroidism treated with conventional therapy, risk of renal disease was associated with an increased calcium-phosphate product level [17]. In addition, two other studies linked elevated serum calcium concentrations with the risk of CKD [4, 6]. Chen et al. recently reported that in a study of patients with chronic hypoparathyroidism, eGFR declined by 8.0 ml/min/1.73 m² in 53 patients treated without recombinant human parathyroid hormone (1–84), rhPTH(1–84), over a 5-year follow-up period [18]. In contrast, eGFR remained stable among 69 patients treated with rhPTH(1–84), suggesting that hormone replacement therapy may ameliorate eGFR decline. However, this analysis was limited by differences in patient management between the cohorts (i.e., rhPTH [1–84]-treated patients were derived from clinical trial studies vs. the control cohort being obtained from an electronic health record database). A possible role for calcium-induced autophagy is suggested, but further research is needed to understand the mechanistic link with the pathogenesis of CKD and chronic hypoparathyroidism [19].

Several limitations should be considered when interpreting findings from this study. Because of the observational study design, there may be unobserved and/or unmeasured differences between the cohorts with and without chronic hypoparathyroidism that were not accounted for in the analyses. As such, we cannot formally exclude the possibility that unknown confounding variables or pathological processes that are unevenly distributed between the cohorts may influence the risk associated with the development of CKD or

decline in eGFR. Kidney transplantation was not an exclusion criterion so we cannot exclude the possibility that this was a confounding factor in the overall results. However, after adjusting for known relevant baseline demographic and clinical characteristics, we found similar results for all outcomes, including the development of incident CKD, CKD stage progression, progression to end stage, and eGFR decline compared with the unadjusted analyses. Unadjusted HR results of the Cox models should be interpreted with caution because of differences in demographic and baseline characteristics between patient cohorts.

In addition, a further potential limitation was the ability to discern whether the decline in CKD was chronic rather than temporary. Misclassification of the outcome is a potential concern in observational studies using administrative databases. Previous studies on the utility of billing codes for identifying CKD have shown relatively low sensitivity but high specificity [20, 21], indicating that patients captured through billing code analysis are unlikely to be false-positives. To ensure that our data show true CKD progression, (1) the definition was based on diagnosis codes or a baseline eGFR measure indicating CKD stage 3 or 4 and (2) we required CKD diagnoses based on an eGFR value that was confirmed with a second eGFR value at least 3 months apart. With this comprehensive definition, we identified events based on both CKD diagnosis codes and by two eGFR values at least 3 months apart (to address the risk that some patients may not have diagnoses of CKD entered into their records). In addition, we conducted sensitivity analyses using CKD diagnosis codes alone to define CKD and CKD progression to address the potential limitation that eGFR values may fluctuate and thus may not indicate chronic renal decline. Results were similar across the main analyses and sensitivity analyses regardless of outcome, which strengthens our overall conclusion.

We used a claims database, which means there may be miscoded or missing data. Although this study was limited to the United States, the conclusions are unlikely to vary across different regions. However, the magnitude of the results may differ by country. Lastly,

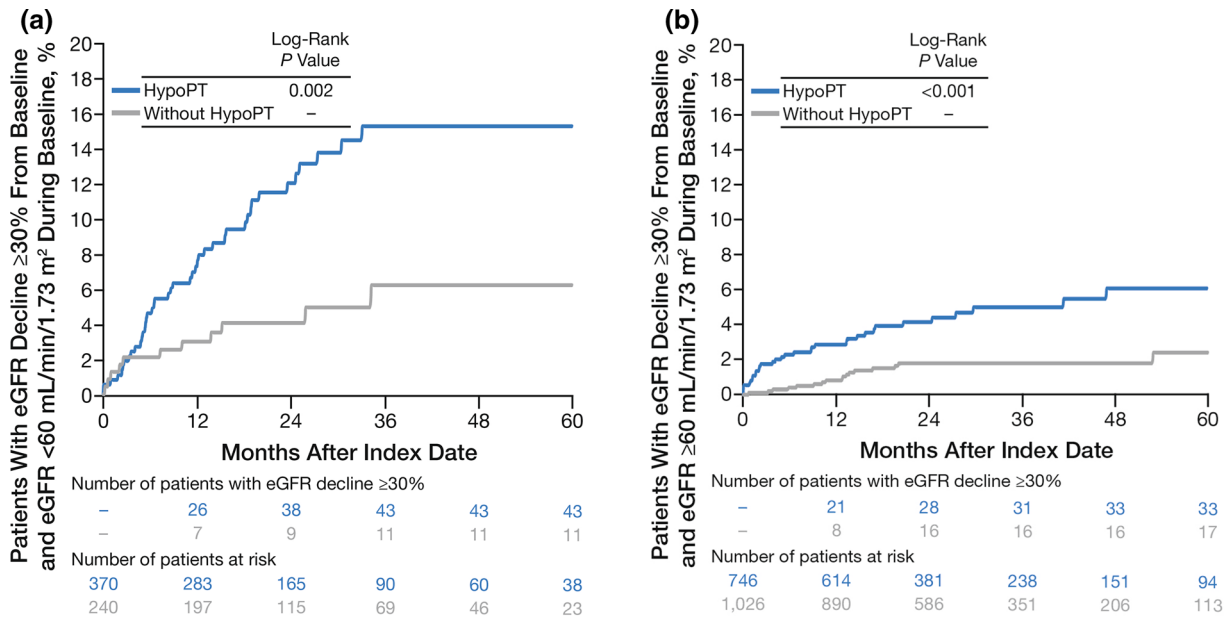


Fig. 4 Time to first eGFR decline $\geq 30\%$ from baseline for patients with eGFR **a** < 60 ml/min/1.73 m² and **b** ≥ 60 ml/min/1.73 m² at baseline. eGFR estimated glomerular filtration rate, HypoPT hypoparathyroidism

because of limited availability of patient-level data for treatments related to hypoparathyroidism (e.g., calcium, vitamins D2 and D3) or other conditions, etiology, duration of disease, and laboratory data, we were unable to assess potential biomarkers or treatments that may mediate the relationship between hypoparathyroidism and renal outcomes. The mechanism of the observed findings merits further research.

Our study has important strengths. Using a nationally representative insurance claims database of patients with chronic hypoparathyroidism, the study evaluated several critical renal outcomes, such as development and progression of CKD assessed by both diagnosis codes and eGFR. Subgroup analyses conducted in cohorts of patients both with and without renal function impairment at baseline also strengthen this study's findings.

CONCLUSIONS

In this large retrospective analysis, chronic hypoparathyroidism was associated with an increased risk of the development of incident

CKD, CKD stage progression, progression to ESKD, and decline in eGFR compared with patients without hypoparathyroidism. The consistent finding that patients with chronic hypoparathyroidism had a significant increased risk of each of these renal complications, across all outcomes and after adjustment for potential confounders, strengthens the conclusions of this study. This study strengthens the evidence regarding the potential impact of chronic hypoparathyroidism on various renal complications and thus has implications for clinical management of hypoparathyroidism, including the need for ongoing monitoring of renal function. Further research is warranted to understand the mechanism(s) responsible for the increased risk of renal complications in patients with chronic hypoparathyroidism and whether disease-specific hormone replacement can ameliorate these risks.

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Compliance with Ethics Guidelines. As this study used de-identified licensed data from a HIPAA-compliant managed care database, ethics committee approval, and informed consent were not required.

Data Availability. The data sets generated during and/or analyzed during the current study from the managed care claims database are not publicly available but are available from the corresponding author on reasonable request.

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