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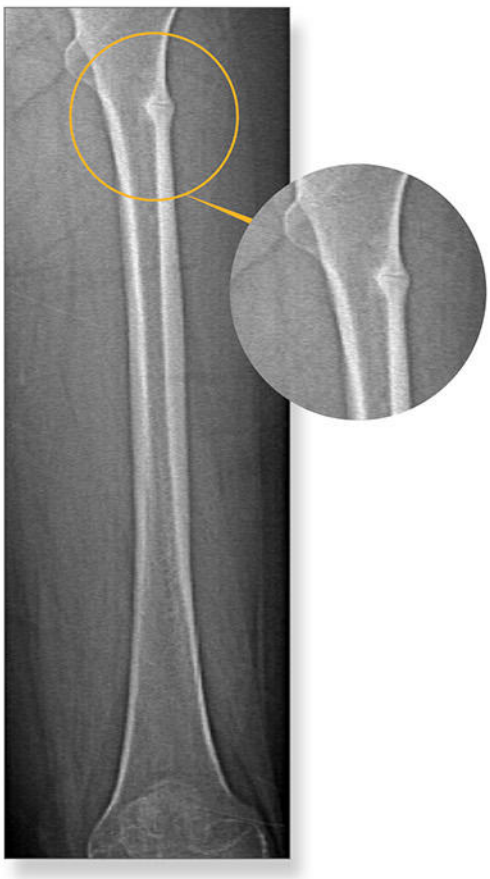

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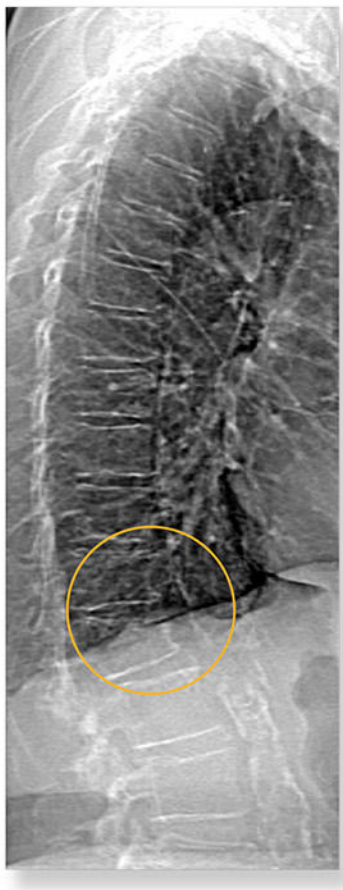

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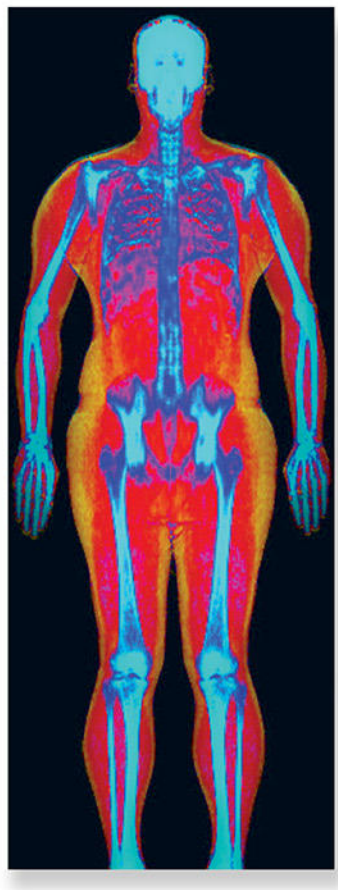

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Hypocitraturia Is an Untoward Side Effect of Synthetic Human Parathyroid Hormone (hPTH) 1-34 Therapy in Hypoparathyroidism That May Increase Renal Morbidity

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ABSTRACT

Subcutaneous human parathyroid hormone (hPTH) therapy can effectively manage hypocalcemia in hypoparathyroidism, with varying effects on hypercalciuria. However, little is known about its ability to decrease the renal comorbidities of hypoparathyroidism: nephrocalcinosis (NC), nephrolithiasis (NL), and renal insufficiency. Urinary citrate (Ucit) promotes the solubility of urinary calcium (UCa); hypocitraturia is a risk factor for NC/NL. Twenty-four–hour UCa, Ucit, and UCa/Ucit were determined in 31 hypoparathyroid subjects receiving hPTH 1-34 therapy for up to 5 years. Before hPTH 1-34, the geometric least squares mean UCa was 346 mg/day (normal <250) and Ucit was 500 mg/day (normal 250–1190); UCa/Ucit was 0.67 mg/mg. After 6 months of hPTH 1-34, UCa decreased (238, $p < 0.001$), but with a greater decrease in Ucit (268, $p < 0.001$), increasing UCa/Ucit, which became significant over time ($p < 0.001$). After stopping hPTH 1-34 and resuming conventional therapy (follow-up; FU), compared to the last measures on hPTH 1-34, Ucit rose to 626 ($p < 0.001$), reducing UCa/Ucit to 0.44, ($p < 0.05$); UCa also rose (273), but was still lower than baseline ($p < 0.05$). Daily hPTH 1-34 dose did not correlate with UCa, but was inversely related to Ucit, and directly related to UCa/Ucit ($p < 0.01$). Mean blood bicarbonate decreased significantly on hPTH 1-34 and remained lower than baseline at FU ($p < 0.01$). Mean eGFR increased on hPTH 1-34 (86 to 96 mL/min/1.73 m^2, $p < 0.001$) and returned to baseline at FU. On renal imaging, 6 subjects did not have NC/NL, 8 had NC/NL prior to hPTH 1-34 that remained unchanged, and 16 developed new-onset ($n = 10$) or progressive ($n = 6$) NC/NL while on hPTH 1-34. Our data demonstrate that treatment with subcutaneous hPTH 1-34 may have an untoward effect of hypocitraturia and high UCa/Ucit ratio that may increase renal morbidity. With increasing use of PTH therapy in hypoparathyroidism, close monitoring and exploration for treatment of hypocitraturia seem warranted. Published 2018. This article is a U.S. Government work and is in the public domain in the USA.

KEY WORDS: PARATHYROID-RELATED DISORDERS; NEPHROCALCINOSIS; NEPHROLITHIASIS; RENAL TUBULAR ACIDOSIS; CITRATE

Introduction

Parathyroid hormone (PTH) is an 84-amino acid peptide produced by the parathyroid glands, with its biological activity residing in the first 34 amino acids. In the kidney, PTH increases urinary phosphate excretion, decreases urinary calcium excretion, and increases 25-OH-vitamin D-1-alpha-hydroxylase activity. In the bone, PTH stimulates calcium release. The net effect of these actions is the regulation of blood calcium levels within a narrow normal range.

Hypoparathyroidism is a deficiency of PTH, leading to hypocalcemia and hyperphosphatemia, and often several renal morbidities including hypercalciuria, nephrocalcinosis (NC), nephrolithiasis (NL), and renal insufficiency. To date, conventional treatment includes oral calcium supplementation and active forms of vitamin D, which may further worsen hypercalciuria and NC/NL, even when serum calcium is maintained slightly below the normal range.[1–3] Previous studies have shown that twice-daily (b.i.d.) subcutaneous (s.c.) injections of synthetic human parathyroid hormone 1-34 (hPTH 1-34) may be used therapeutically to prevent hypocalcemia in hypoparathyroidism.[4,5] However, it has not been consistently shown to decrease hypercalciuria, and there are no long-term data assessing its ability to decrease the renal comorbidities of hypoparathyroidism.

Urinary citrate promotes the solubility of urinary calcium.[6] Hypocitraturia is a known risk factor for the development of renal calcification. Furthermore, metabolic acidosis reduces

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renal excretion of citrate, which may lead to increased NC/NL.[6] Impaired urinary acidification, leading to proximal renal tubular acidosis, is a known effect of excess PTH, both experimentally and in primary hyperparathyroidism.[7,8] However, the prevalence of hypocitraturia in hypoparathyroid patients treated with hPTH 1-34 is unknown.

Subjects and Methods

Subjects

Thirty-two patients (7 men, 25 women), mean (range) age 39.5 (16 to 60) years, with hypoparathyroidism for >1 year, were enrolled in a study started in 2006 evaluating the effects of 5 years of hPTH 1-34 replacement therapy. The etiology of hypoparathyroidism included postsurgical (20 patients), activating mutation of the calcium-sensing receptor (CaSR) (4 patients), 22q11.2 deletion syndrome (2 patients), hypoparathyroidism–deafness–renal syndrome (2 patients), and idiopathic/acquired autoimmune (4 patients). Subjects were excluded from enrollment if they had significant liver or kidney disease, chronic disease known to affect mineral metabolism, a history of chronic steroid or bisphosphonates use, active thyroid cancer, or pregnancy. One subject with hypoparathyroidism–deafness–renal syndrome who did not have urinary citrate measurements was excluded from analysis. The Institutional Review Board of the National Institute of Dental and Craniofacial Research (NIDCR) approved this protocol. Written informed consent was obtained from adult subjects or the parents of adolescent subjects; written assent was obtained from the adolescents and they were reconsented after turning 18 years old.

Therapy of hypoparathyroidism

Following an optimization period on conventional therapy, calcitriol was discontinued and subjects were started on b.i.d. ($n = 29$) or three times daily (t.i.d.; $n = 2$) s.c. injections of synthetic human hPTH 1-34, beginning the morning after the last dose of calcitriol. The study was initially designed to compare b.i.d. with t.i.d. dosing, with subjects being randomly assigned to a treatment group. However, in 2010, the study was redesigned such that the two subjects on t.i.d. dosing were switched to b.i.d. dosing 30 months into treatment; all subsequent subjects were started on b.i.d. injections.

hPTH 1-34 lyophilized powder was purchased from Bachem, Inc. (Torrance, CA, USA) and then prepared and packaged by the NIH Pharmaceutical Development Service as described.[9] The mean ± SD starting dose was 0.40 ± 0.06 μg/kg/day in the b.i.d. subjects and 0.47 ± 0.04 μg/kg/day in the t.i.d. subjects. However, the doses were rapidly adjusted as needed to maintain the serum calcium level at or slightly less than the lower limit of normal (7.6 to 9 mg/dL, 1.9 to 2.25 mmol/L). Calcium intake, through diet or supplements while on hPTH 1-34, was targeted at 1000 to 2000 mg/day; patients with low or irregular dietary calcium intake also took calcium supplements. Subjects found to be vitamin D-deficient were treated with ergocalciferol or cholecalciferol to maintain the 25-hydroxyvitamin D level above 62.5 nmol/L (25 ng/mL). No subjects were taking active forms of vitamin D.

Monitoring

Subjects were evaluated at the Clinical Center of the NIH (Bethesda, MD, USA) every 6 months. After the last visit on hPTH 1-34, the drug was weaned as previously described,[10] with all subjects resuming conventional therapy with calcium and calcitriol. Subjects then returned to the NIH for a follow-up visit (FU) 6 to 12 months after the last visit on hPTH 1-34. Testing at NIH included urine pH, two 24-hour urinary measurements for calcium (UCa) and citrate (Ucit), and fasting measurement of routine blood biochemistries. The average of the two urine measurements was used for analysis, unless only one collection was available, in which case the single measure was used; in a few measures, urine pH was only available on a random morning sample. The majority of 24-hour urine collections were performed during inpatient admissions under nursing supervision. Urine creatinine excretion was measured to ensure collection adequacy; if a collection was questionable, it was excluded from analysis. Between visits to the NIH, blood mineral metabolism was monitored at least once a month per protocol at the subjects' local laboratories and therapy was adjusted to maintain the serum calcium level at or slightly below the lower limit of normal noted above. A renal ultrasound (US) was performed at baseline, annually, and at the FU visit. Renal computed tomography (CT) without contrast was performed at baseline and then annually. Urinary citrate measurements were formally added when the study was redesigned in 2010; thus, pre-hPTH 1-34 (baseline) and 6-month citrate values were unavailable for seven subjects. Baseline renal ultrasounds were unavailable for two subjects. However, one of these subjects had a normal renal US at first assessment and was therefore assumed to be normal at baseline. The other had moderate/severe NC at first US assessment (18-month visit), suggesting that NC was likely to be present at baseline. Scans were read by NIH radiologists who were not directly involved with the patients and were not aware of the therapy at the time of study.

Treatment of hypocitraturia

Based on the unexpected observation of reduced urinary citrate and increased urine calcium/citrate (UCa/Ucit) ratios in several patients, which was judged as a risk for NC/NL, the protocol was revised in 2014 to add potassium citrate, 30 to 60 meq/day as adjuvant therapy for subjects with ratios >0.7 mg/mg. Although there are no published data in patients with hypoparathyroidism establishing the use of the UCa/Ucit as a measure to guide therapy, we selected this cutpoint for treatment as a conservative measure, given that the upper limit of normal for UCa and the lower limit for Ucit excretion is approximately 200 to 300 mg/day (ie, UCa 200 mg/Ucit 300 mg = 0.67 mg/mg). Fourteen subjects received potassium citrate at some point in the study. In two patients, potassium citrate was discontinued because of gastrointestinal intolerability. The consent form was revised informing patients of the potential risk of hypocitraturia, and all enrolled subjects were reconsented at their next scheduled visit.

Statistical analysis

All statistical analyses were performed in SAS version 9.3 (SAS Institute, Cary, NC). Statistical significance was assumed at $\alpha = 0.05$. Corrections were made for multiple comparisons using Fisher's protected LSD with additional Bonferroni corrections when the overall main effects were not significant. As this was a small study with very few men, subanalyses based on sex were not performed. Unless otherwise stated, results are presented as mean ± SE. The biochemical findings were analyzed using mixed models repeated measures analysis (Proc Mixed; SAS Institute)

with pairwise post hoc comparisons focusing on four time points: prior to hPTH 1-34 (baseline), 6 months on hPTH 1-34, last measure on hPTH 1-34, and post-hPTH 1-34 (FU). The mixed models analyses of the 24-hour urinary excretions of calcium (UCa), citrate (Ucit), and calcium/citrate ratios (UCa/Ucit) required log-transformation to normalize their distributions. The mixed models analysis of urine pH was adjusted by adding a binomial covariate for the administration or lack of administration of potassium citrate during the period of the study visit.

For exploring the relationship between NC/NL and 24-hour urinary parameters (UCa, Ucit, and UCa/Ucit), subjects were grouped by on-study changes in NC/NL status into three groups: "No NC/NL," "Stable NC/NL," and "New/Progressing NC/NL." Each subject's geometric means of urinary parameters at each visit were calculated (subject-level geometric means); the overall geometric means of these subject-level geometric means were calculated separately for each NC/NL status. One subject who had mild NL at baseline that resolved during the study was excluded as that would have required inclusion of a fourth category including only one subject. ANOVA (log-scale) was used to test for differences in the subject-level geometric means among the three NC/NL status groups with respect to the urinary parameter. Univariate logistic regressions were performed on each subject's mean 24-hour urine volume (averaged across all treatment visits) and the maximum observed UCa/Ucit (also based on the full set of a subject's observed data on treatment) to test their effects on the development of renal calcifications. Additionally, quartiles of UCa/Ucit were determined for the four time points and renal imaging status.

A mixed-models regression of the log-transformed UCa, Ucit, UCa/Ucit ratios, and blood bicarbonate over the total daily hPTH dose was used to examine that relationship. The mixed-models regression included a random effect for subject and assumed compound symmetry. Any time-point when the hPTH dose was 0 was excluded from the mixed-model regressions. Similar regressions were also performed to examine the relationship between Ucit and blood chloride with blood bicarbonate.

Results

The mean (range) duration of hPTH 1-34 therapy was 37.1 (7.5 to 63.9) months. Eight subjects completed the full 5 years of therapy per the protocol; the remaining 23 discontinued early for the following reasons: pregnancy (1 subject); bone pain (3 subjects); decreased radial BMD (2 subjects); noncompliance with study procedures (1 subject); acquired lack of responsiveness to hPTH 1-34 therapy (1 subject); inconvenience (1 subject); partial parathyroid recovery (1 subject); and early termination of study because of the unanticipated closure of the NIH Pharmaceutical Development Service (13 subjects). Because of the wide variability in treatment duration, analyses were focused on the four time-points described above. Twenty-five subjects (81%) returned for the FU off hPTH 1-34.

Biochemical findings

At the four time-points analyzed, geometric least squares mean (LSM) 24-hour UCa excretion on conventional therapy was elevated at baseline and declined during hPTH 1-34 therapy. At FU, UCa had increased, but was still lower when compared to baseline (Fig. 1*A*). Geometric LSM Ucit excretion was within the normal range at baseline (Fig. 1*B*). At the 6-month visit, the Ucit was statistically decreased from baseline, and remained lower for the duration of hPTH 1-34 therapy, returning to baseline levels at FU (Fig. 1*B*). As the drop in Ucit was greater than the drop in UCa, UCa/Ucit increased during hPTH 1-34 therapy. Although this increase was not statistically significant at 6 months compared to baseline, the change in UCa/Ucit became significant over time; the ratio was lower at FU compared to the 6-month and last-treatment visits (Fig. 1*C*, $P < 0.001$). At baseline 9 of 24 subjects (38%) had UCa/Ucit $>$ 0.7 mg/mg, increasing to 23 of 31 patients (74%) with UCa/Ucit $>$0.7 mg/mg while on hPTH 1-34, dropping back down to only 4 of 25 subjects (16%) at FU. Of the 23 subjects with UCa/Ucit $>$0.7 mg/mg while on hPTH 1-34, only 14 subjects received potassium citrate therapy at some time during the study, as this adjuvant therapy was added to the study several years after study initiation. Despite this, only 4 of 14 subjects on potassium citrate therapy during their last visit on hPTH 1-34 had reduction of the UCa/Ucit ratio to $<$ 0.7 mg/mg; mean UCa/Ucit ratios were not different between the potassium citrate-treated and untreated subjects. At FU, eight subjects were still taking potassium citrate. Individual data for the 31 subjects studied can be found in Supplemental Table 1. One patient with an activating mutation of the CaSR was also treated with a thiazide because of hypercalciuria.

At baseline, mean fasting blood levels of calcium and phosphate were 8.27 ± 1.04 mg/dL (2.07 ± 0.03 mmol/L) and 4.68 ± 0.12 mg/dL (1.5 ± 0.04 mmol/L); these measures, as well as urinary phosphate excretion (data not shown), were not significantly different at the four time-points. The blood bicarbonate decreased while on hPTH 1-34 therapy and, despite remaining within the normal range, it was significantly decreased at FU (Fig. 1*D*). No correlation was found between blood bicarbonate and Ucit or hPTH 1-34 dose. There was suggestion of a negative correlation between blood bicarbonate and chloride, which would support a proimal tubule effect; however, this was not statistically significant ($p = 0.079$). Urine pH, adjusted for potassium citrate administration per the methods, was increased compared to baseline at the last measure on hPTH 1-34 and was still increased at FU (Fig. 1*E*). The statistical model's adjustment for the administration of potassium citrate was estimated to increase urine pH by only 0.12 ± 0.204 ($p = 0.57$). The mean eGFR increased while on hPTH 1-34 therapy and returned to baseline at FU (Fig. 1*F*). Mean data at each NIH visit can be found in Supplemental Figure 1.

The total daily hPTH 1-34 dose was not correlated with UCa ($p = 0.6$), but was negatively correlated with Ucit excretion (log-linear regression slope $\pm$ SEM: -0.006 ± 0.002, $p < 0.01$) and positively correlated with UCa/Ucit (0.007 ± 0.003, $p < 0.01$). Endogenous PTH levels were not related to total hPTH 1-34 doses, UCa, Ucit, or UCa/Ucit ratios.

Renal imaging findings

Prior to hPTH 1-34 therapy, 16 of 31 subjects had normal renal CT and US, whereas 15 of 31 subjects had evidence of NC and/or NL on renal US and/or CT. Six subjects from the total cohort (19%) maintained normal imaging throughout the study. Eight subjects (26%) had NC/NL at baseline, which did not appear to change significantly during hPTH 1-34 treatment. One subject (3%) had mild NL at baseline that resolved during the study. The remaining 16 subjects (52%) either developed new-onset ($N = 10$) or worsening ($N = 6$) NC/NL during hPTH 1-34 therapy (Fig. 2). Resolution of new NC/NL was seen in one of these subjects, but persisted in the rest. Urine parameters with respect

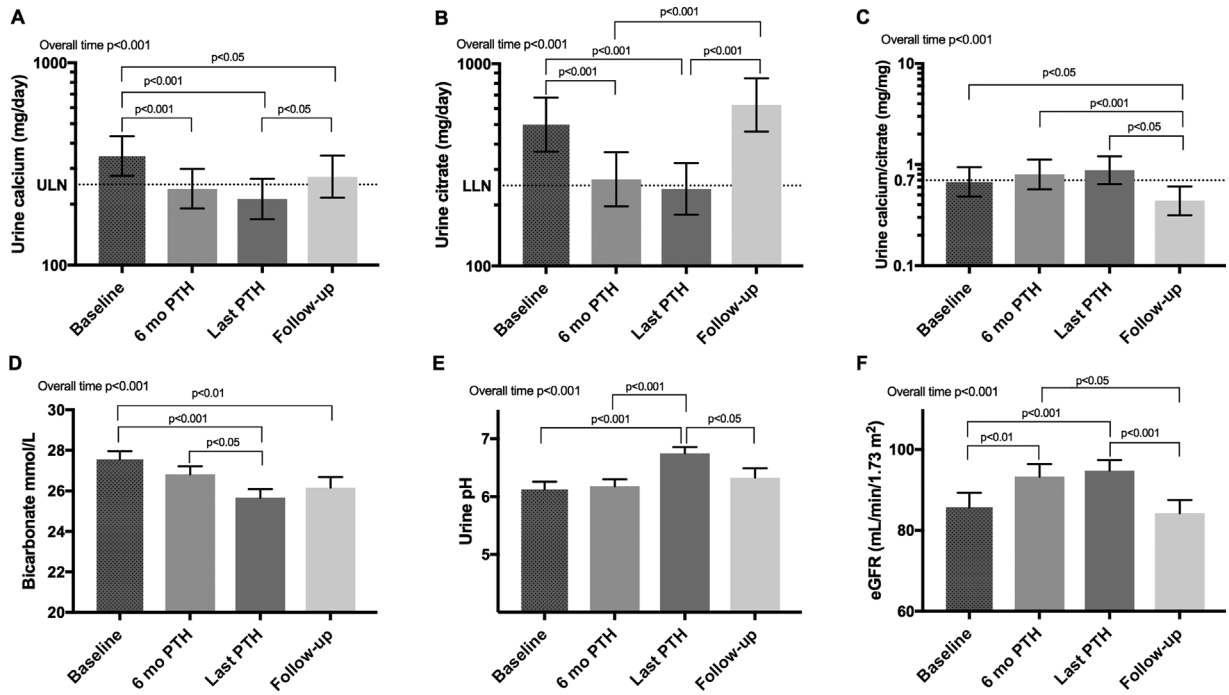

Fig. 1. Biochemical measures at baseline, 6 months on hPTH 1-34, last measure on hPTH 1-34, and follow-up. Geometric LSM with 95% confidence limits for (**A**), 24-hour urine calcium excretion (ULN = 250 mg/day); (**B**) 24-hour urine citrate excretion (LLN = 250 mg/day); (**C**) 24-hour urine calcium/citrate ratio (threshold for potassium citrate therapy >0.7 mg/mg). Mean ± SE for (**D**) blood bicarbonate (normal range 22 to 29 mmol/L); (**E**) urine pH (normal range 5 to 8); (**F**) eGFR = normal >90 mL/min/1.73m^2. hPTH = human parayhyroid hormone; ULN = upper limit of normal; LLN = lower limit of normal; eGFR = estimated glomerular filtration rate.

to renal imaging findings are shown in Fig. 3. Although there was the suggestion that Ucit was lower and UCa and UCa/Ucit ratio were higher in those with stable or new disease (Fig. 3*A–C*), these differences were not statistically significant. Additionally, univariate logistic regression analyses suggested that the maximum observed UCa / Ucit ratio best predicted the NC/NL status; however, this did not reach statistical significance ($p = 0.059$). Supplemental Table 2 shows the different quartiles

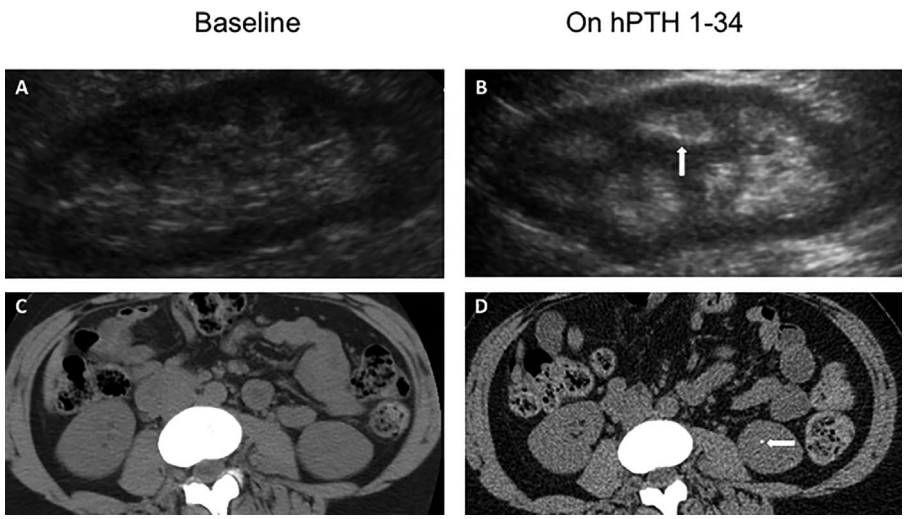

Fig. 2. Renal imaging in hypoparathyroid subjects treated with human parathyroid hormone (hPTH) 1-34. Top panels: (**A**) normal renal ultrasound in a 40-year-old man with hypoparathyroidism due to an activating mutation of the calcium-sensing receptor (CaSR) on conventional therapy for over 20 years; (**B**) medullary nephrocalcinosis (arrow) is seen after 1 year of hPTH 1-34 (Subject #16 in Supplemental Table 1). Bottom panels: **(C)** normal renal CT in a 34-year-old woman with postsurgical hypoparathyroidism on conventional therapy for 6 years; (**D**) asymptomatic nephrolith seen (arrow) after 3 years of hPTH 1-34 (Subject #3 in Supplemental Table 1).

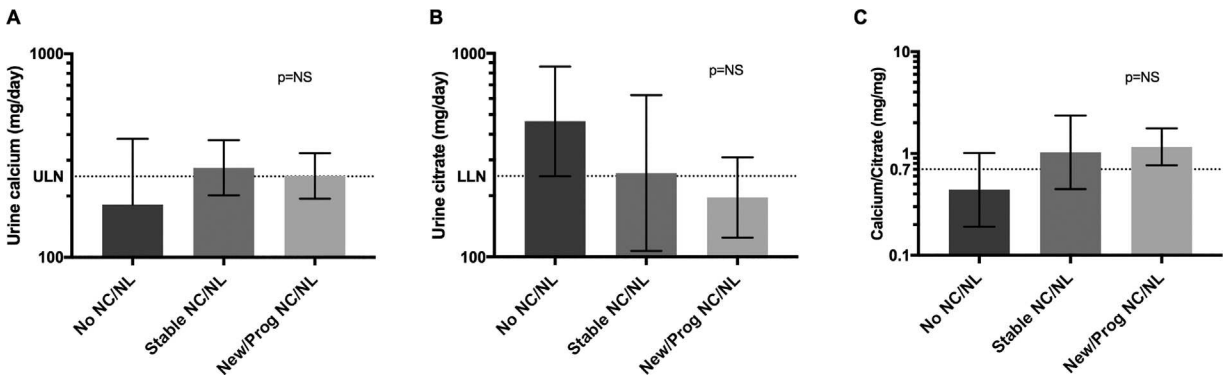

Fig. 3. Urine parameters based on imaging findings. Geometric means with 95% confidence limits for (**A**) 24-hour urine calcium excretion (ULN = 250 mg/day); (**B**) 24-hour urine citrate excretion (LLN = 250 mg/day); (**C**) 24-hour urine calcium/citrate ratio (threshold for potassium citrate therapy >0.7 mg/mg). ULN = upper limit of normal; LLN = lower limit of normal; NC/NL = nephrocalcinosis/nephrolithiasis.

for UCa/Ucit by study visit and renal imaging status. As this was a small study, definitive UCa/Ucit ratio cutpoints predicting the development of NC/NL could not be determined. Twenty-four–hour urine volume did not have a significant effect on NC/NL development or progression ($p = 0.3$).

Discussion

Human synthetic PTH 1-34 treatment in patients with hypoparathyroidism reduced Ucit excretion and increased UCa/Ucit ratios. As hypocitraturia is a known risk factor for nephrocalcinosis and nephrolithiasis in otherwise healthy individuals and those with other metabolic conditions,[6,11–13] it is possible that this alteration in citrate metabolism with hPTH 1-34 therapy potentially contributed to the development or worsening of NC/NL in 52% of the subjects in this study.

Citrate is a weak acid, sourced from ingested food or the tricarboxylic acid cycle, that circulates in the blood as either a weak trivalent anion or is complexed to cations. It is readily absorbed in the small intestine and is filtered at the glomerulus. There is no tubular secretion of citrate; however, citrate reabsorption occurs in the proximal tubule via sodium-dependent dicarboxylate transporters, resulting in excretion of approximately 10% to 35% of the filtered load.[14,15] In the urine, citrate forms soluble complexes with calcium, thus reducing the ionic calcium concentration and the urinary saturation of calcium oxalate and calcium phosphate. This, in turn, inhibits the nucleation and crystal growth of calcium oxalate and calcium phosphate. There are many factors that affect citrate excretion. In general, states of acidosis based on metabolic conditions, protein intake, medications, and hypokalemia result in decreased citrate excretion.[6,14–17] Conversely, alkalosis increases citrate excretion. The definition of hypocitraturia is ill-defined, with some proposing absolute excretion cut-off and others using calcium/citrate, citrate/calcium, and citrate/creatinine ratios.[18–21] As hypercalciuria is an important comorbidity of hypoparathyroidism and its therapy, we chose to focus on the UCa/Ucit ratio, with the understanding that the risk for renal calcification is more likely related to the relative concentrations of these two analytes, rather than their absolute excretion. For the initiation of potassium citrate therapy, we selected a ratio cut-off of 0.7 mg/mg based on the normal upper and lower limits for calcium and citrate excretion and supported by a report demonstrating that pediatric recurrent stone-formers have been shown to have a mean UCa/Ucit ratio of 0.64 mg/mg.[21]

The effects of hypercalciuria and PTH on renal citrate excretion have been studied in animal and human models. Blood calcium concentration and UCa excretion correlate directly with blood citrate concentration and Ucit excretion,[22,23] with the increase in citrate presumably a compensatory response to prevent calcium crystal formation. In healthy individuals, there is a negative correlation between urinary citrate excretion and endogenous PTH levels.[15] Experimentally, the injection of PTH causes bicarbonaturia with a resultant increased urinary pH, ie, a proximal renal tubular acidosis, resulting in the lowering of serum bicarbonate.[7] Thus, one might expect to find hypocitraturia in patients with primary hyperparathyroidism, who are presumed to have renal stones due to hypercalciuria. Blood citrate levels have been shown to be higher in hyperparathyroidism and lower in hypoparathyroidism,[22] and parathyroidectomy appears to correct bicarbonate wasting in hyperparathyroidism.[8] However, the data in hyperparathyroidism are variable in studies comparing stone-formers with non-stone-formers, ranging from lower UCa and Ucit in non-stone formers,[24] higher UCa in stone-formers but no differences in Ucit,[25] and no significant differences in UCa, Ucit, or blood calcium between groups.[26] One study showed higher UCa and oxalate in stone-formers and, though Ucit excretion was directly correlated with UCa, hypocitraturia was not associated with an increased odds ratio for stone formation.[27] It is likely these conflicting findings are, in part, because only absolute 24-hour excretion values were considered and not the UCa/Ucit ratio. For example, Berger and colleagues demonstrated a significant decrease in UCa excretion in 27 patients after parathyroidectomy with a modest nonsignificant decrease in urinary citrate[26]; however, review of their data indicates that the UCa/Ucit decreased 40% after surgery. To date, there have been no reports of Ucit in patients with hypoparathyroidism treated with PTH 1-34 or PTH 1-84.

In our study, we demonstrated a robust citrate excretion in the face of hypercalciuria at baseline; both UCa and Ucit decreased with hPTH 1-34 therapy. However, the decrease in Ucit was more dramatic than the decrease in UCa, despite potassium citrate therapy in almost half of the subjects, resulting in an increase in the UCa/Ucit ratio while on hPTH 1-34. After hPTH 1-34

discontinuation, Ucit returned to baseline levels and, though urine calcium rose compared to the last measure on treatment, it was still significantly lower than baseline values. The UCa/Ucit at FU dropped compared to on-hPTH 1-34 values and was also lower than baseline values. These findings suggest that the decrease in Ucit was likely due to the hPTH 1-34 therapy, rather than simply the decrease in urine calcium. That the total daily hPTH 1-34 dose did not correlate with UCa excretion, but was inversely related to Ucit and directly related to the UCa/Ucit ratio further supports this. The changes in urine pH and blood bicarbonate indicate that hPTH 1-34 likely induced a mild or compensated renal tubular acidosis, as seen by the changes in serum bicarbonate. It is unknown if the mild persistence of these changes at FU are due to prolonged transient or permanent effects at the tubule. Given that hypocitraturia is a well-known cause of nephrocalcinosis and nephrolithiasis, it is probable that the relative hypocitraturia contributed to the development of new or progressive renal calcifications in 52% of subjects despite a decrease in renal calcium excretion. Notwithstanding this increase in renal calcifications, we surprisingly observed a statistically significantly increase in eGFR on hPTH 1-34 that returned to baseline after discontinuation.

This study is limited by the lack of a placebo or control group and a small number of subjects, with multiple etiologies of hypoparathyroidism, treated with hPTH 1-34 for varying lengths of time. Other urine analytes associated with renal calcifications, such as oxalate and uric acid, were not systematically measured. Conventional therapy with calcium and calcitriol may not have been fully optimized in all subjects prior to starting hPTH 1-34, resulting in a higher UCa level at baseline compared to FU. As Ucit was added to the protocol at a later stage, baseline and 6-month Ucit values are missing in seven subjects. Likewise, six subjects did not return for FU. However, the robust changes seen in the urine parameters at the last measure on hPTH 1-34 and FU suggest that the addition of these data would likely strengthen the findings. Although the trend in urinary results suggested a relationship with the risk of developing new or progressive calcifications, this did not reach statistical significance; significance may have been achieved with a larger number of subjects and a control group. Our data may also have been confounded by the addition of potassium citrate therapy in 14 subjects. However, we felt medically obligated to offer treatment to these patients and did not observe significant differences in Ucit values in those treated with potassium citrate. When it became apparent that hypocitraturia was directly related to initiation of hPTH 1-34, all patients were presented with this new risk and reconsented; no subjects elected to discontinue hPTH 1-34 therapy for this reason. Given this confounder, it is possible that the hypocitraturia and increase in the UCa/ Ucit ratio we observed may have been even more significant, had we chosen not to initiate potassium citrate therapy.

This is the first study to demonstrate that in patients with hypoparathyroidism, twice daily hPTH 1-34 therapy was associated with reduced UCa and Ucit excretion, increased UCa/Ucit, decreased serum bicarbonate, and increased eGFR. The decrease in Ucit was inversely correlated with the total daily hPTH 1-34 dose, suggesting a direct hPTH 1-34 effect on citrate metabolism in these patients. Despite a reduction in UCa excretion, new or worsening NC/NL developed in 52% of subjects, which may have been due to relative or absolute hypocitraturia. Although it is unknown if these conclusions are generalizable to recombinant hPTH 1-84, like findings may be expected given the similarity in biological activity at the renal tubule. Thus, with increasing use of recombinant PTH 1-34 and PTH 1-84 for the treatment of hypoparathyroidism, monitoring and possible treatments for hypocitraturia and renal calcification seem warranted.

Disclosures

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