CLINICAL TRIAL

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Calcium Citrate Versus Calcium Carbonate in the Management of Chronic Hypoparathyroidism: A Randomized, Double-Blind, Crossover Clinical Trial

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ABSTRACT

In hypoparathyroidism (HypoPT), calcium supplementation is virtually always required, although the disease is likely to be associated with an increased risk of nephrolithiasis. The use of calcium citrate (Ca-Cit) theoretically could have a positive impact on the nephrolithiasis risk because citrate salts are used to reduce this risk. Our objective was to evaluate the potential therapeutic advantage of Ca-Cit in comparison with calcium carbonate ($CaCO_3$) in HypoPT, on nephrolithiasis risk factors, as well as to their ability to maintain desirable serum calcium levels. We also evaluated these preparations on quality of life (QOL). This randomized, double-blind, crossover trial recruited 24 adults with postsurgical chronic hypoparathyroidism at Campus Bio-Medico University of Rome. Participants were randomized 1:1 to Ca-Cit or $CaCO_3$ for 1 month and then crossed over to the other treatment for another month. The primary outcomes were changes in albumin-adjusted serum calcium and in ion activity product of calcium oxalate levels (AP[CaOx] index). Secondary efficacy outcomes included changes in SF-36 survey score, fatigue score, constipation, and adverse events. No difference in terms of AP(CaOx) index was observed between the two groups. However, Ca-Cit was associated with a significant reduction in the oxalate/creatinine ratio compared with $CaCO_3$ (−2.46 mmol/mol [SD 11.93] versus 7.42 mmol/mol [SD 17.63], $p = 0.029$). Serum calcium and phosphorus concentration was not different between the two calcium preparations. Ca-Cit was associated with less constipation ($p = 0.047$). No difference was found in QOL scores. Although Ca-Cit did not modify the AP(CaOx) index when compared with $CaCO_3$, it was associated with a reduction in urinary oxalate excretion that could have a potential beneficial effect on nephrolithiasis risk. These results are likely to have clinical implications in HypoPT, particularly those who do not tolerate $CaCO_3$ and those affected by nephrolithiasis. A longer-term experience is needed to confirm these findings. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: HYPOPARATHYROIDISM; CALCIUM CITRATE; CALCIUM CARBONATE; PTH; NEPHROLITHIASIS

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Introduction

Hypoparathyroidism (HypoPT) is defined by hypocalcemia and undetectable or insufficient levels of parathyroid hormone (PTH). According to international guidelines,[1-3] standard treatment of HypoPT includes oral calcium salts and active vitamin D metabolites to prevent hypocalcemia and to maintain serum calcium levels in the low-normal range or just below normal.

Calcium carbonate ($CaCO_3$) is the most widely used preparation to treat HypoPT because it contains the highest percentage of elemental calcium on a molecular weight basis (eg, 42%) and is the least expensive. It requires a source of acid, either gastric hydrochloric acid or an acidic element in the diet (eg, protein). The acid converts the carbonate salt to carbonic acid that immediately is converted to water and carbon dioxide (CO_2).[4] It is the production of CO_2 that is believed to be responsible for side effects such as flatulence, constipation, bloating, and other gastrointestinal symptoms.

These inconvenient clinical issues with $CaCO_3$ raise the question about whether another calcium preparation might be more advantageous in HypoPT. Calcium citrate (Ca-Cit) is one such alternative because it has a solubility at higher pH levels (>6.5) and does not therefore require gastric acid for absorption. It is, thus, generally recommended in patients with achlorhydria or who are receiving proton pump inhibitors (PPI). Its bioavailability irrespective of food is another advantage over $CaC0_3$.[5]

Another potential advantage of Ca-Cit in HypoPT is that citrate salts are used in the treatment of nephrolithiasis, since they have shown an inhibitory effect on kidney stone formation because the most frequent kidney stones consist of 70% to 80% calcium oxalate.[5,6] Since patients with HypoPT are at risk for kidney stones,[7,8] Ca-Cit may harbor this additional therapeutic benefit. Up to now, there are no studies aimed to investigate the efficacy of Ca-Cit in the management of subjects with chronic HypoPT.

This study was conducted to directly compare the use of $CaCO_3$ and Ca-Cit in HypoPT. We aimed to investigate, in subjects with chronic HypoPT, (i) the effect of Ca-Cit on elements that contribute to risk of nephrolithiasis, (ii) the ability of Ca-Cit to maintain normal serum calcium levels compared with $CaCO_3$, and (iii) its impact on quality of life (QOL).

Materials and Methods

Study design and population

This randomized, double-blind, crossover, single-center study was conducted from October 2019 to April 2020. Subjects with postsurgical chronic HypoPT were consecutively screened at the bone outpatient clinic of Fondazione Policlinico Universitario Campus Bio-Medico. The diagnosis of postsurgical chronic HypoPT was established at least 6 months after surgery based on clinical and biochemical features (low or inappropriately normal PTH levels with low calcium levels on at least two prior occasions separated by an interval of at least 30 days).

All patients underwent thyroidectomy for differentiated thyroid cancer, nontoxic goiter, or Graves' disease. Subjects who were initially included met the following criteria: men or women, aged 18 to 75 years; no change of treatment (calcium supplements: calcium carbonate and active vitamin D) over a 3-month period before enrollment; stable serum calcium and phosphorus concentrations and absence of hypocalcemic symptoms over the 3 months before enrollment; and a requirement for active vitamin D (calcitriol ≥0.25 mcg daily) and oral calcium (≥1000 mg daily). All subjects had 25OHD values higher than 20 ng/mL, as suggested by the European Society of Endocrinology guidelines for the management of hypoparathyroidism.[2]

We excluded patients with clinical history and/or US evidence of kidney stones, liver or renal failure (glomerular filtration rate [GFR] <30 mL/min), hypercalcemia detected in the last year, hyperthyroidism from any cause, other calcium metabolism disorders, and/or using the following drugs within 12 months from the beginning of the study: diuretics, calcitonin, corticosteroids, anabolic steroids, anticonvulsants, H_2 receptor antagonists or proton pump inhibitors, and bone active therapies such as bisphosphonates, denosumab, and teriparatide. Finally, smokers (>10 cigarettes/d) and those with alcohol intake (>70 mL/d) were also excluded.

Ethics and institutional review board approval

The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Principles of Good Clinical Practice. The research protocol was approved by local ethics committees, and all participants gave written informed consent allowing their anonymized information to be used for a data analysis.

Randomization and masking

In this double-blind, crossover study, each participant was evaluated during two phases, the order of which was randomized. The two phases were drug A (Ca-Cit) and drug B ($CaCO_3$). Each phase lasted 1 month, during which participants took study medications and were evaluated every 2 weeks.

Starting 1 week before randomization and during the entire study period, all patients were instructed to adhere to a special diet at home. Under the supervision of a dietician, each subject received a diet containing sufficient calcium to reach a dietary daily intake of 1200 mg, including the amount coming from high-calcium mineral water, a low-normal quantity of animal protein (0.8 g of protein per kg of body weight), a reduced amount of oxalate (mean intake of 50 mg oxalate/daily) and salt (mean intake of 50 mmol sodium/daily). All patients were advised to maintain a fluid intake of 2 L/d (water with sodium concentration of 5.1 mg/L and calcium concentration of 305 mg/L).

A statistician not directly involved in the trial allocated subjects by use of computer-generated randomization. Randomization to Ca-Cit or $CaCO_3$ was double-blind (ie, patients, investigators, and those assessing outcomes were masked to study drugs). We randomly allocated patients who fulfilled the selection criteria 1:1 to Ca-Cit or $CaCO_3$, for 1 month, and then the patients crossed over to the other treatment for another month. The initial total amount of elemental calcium was the same amount that they had taken before the study enrolment. The total amount of elemental calcium was divided in two or three doses (each dose immediately after meal). The dose of active vitamin D was equal to the daily dose taken before the study and was not changed during the study period. At the time of crossover (from drug A to drug B or from drug B to drug A), patients received the same total amount of elemental calcium that they had taken during the last week of phase 1. Medication containers were labeled with a unique number representing the randomly allocated study sequence. Both Ca-Cit and $CaCO_3$ tablets had identical appearance, smell, and taste. Each tablet

consisted of 250 mg elemental calcium. Furthermore, the calcium supplementation dosage was changed based on the albumin-adjusted serum calcium values as suggested below: if the albumin-adjusted serum calcium value was less than 8 mg/dL, the dose of calcium was increased by 500 mg of elemental calcium with a new dosage of calcium on blood sample after 48 hours, up to the achievement of normocalcemia. If the subject had serum albumin-adjusted calcium between 8 mg/dL and 9 mg/dL (optimal range) with signs and/or symptoms of hypocalcemia, calcium supplementation was increased by 500 mg of elemental calcium. If instead, the albumin-adjusted calcium value was higher than 10.4 mg/dL, the dose of calcium was reduced by 500 mg of elemental calcium with a new dosage of calcium on blood sample after 48 hours, up to the achievement of normocalcemia.

Procedures

Clinical evaluation

We evaluated the clinical profile of the whole study population by recording the medical history and by reviewing the clinical, laboratory, and imaging results already performed on patients. Physical examination was performed on all subjects at each visit during the study period by an expert physician. Signs of hypocalcemia, such as Chvostek's or Trousseau's signs, were assessed at each visit. At each visit, constipation was evaluated through the ROME III functional constipation criteria.[9] At each visit, adherence was assessed by pill counts. Gastrointestinal tolerance was recorded at each visit by using an instrumental question with a 10-point visual analog scale (VAS). Absence of nephrolithiasis was documented retrospectively and by review of medical records (all subjects were tested by kidney ultrasound within 6 months before enrollment).

QOL evaluation

QOL was evaluated at each visit during the study period using the SF-36 (version 1)[10] and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score (version 4).[11] SF-36 assesses patient health across 36 items that are grouped into eight domains: bodily pain, general health perceptions, mental health, physical functioning, role limitations due to emotional functioning, role limitations due to physical functioning, social functioning, and vitality. From the eight individual subscales, two component summary scores were generated for the physical component summary (PCS) and mental component summary (MCS) scores. Several validated tools are available for the measurement of fatigue, but no gold standard has been defined. The FACIT-fatigue is a short, 13-item fatigue subscale that determines an individual's level of fatigue during usual daily activities over the past week. Each question is scored on a four-point Likert scale (4 = not at all fatigued to 0 = very much fatigued), with a higher total score indicating a better QOL.

Biochemical analysis

Fasting blood sampling was obtained in the morning (from 8:00 to 8:30 a.m.) before calcium supplementation. All biochemical parameters (serum total calcium, phosphorus, albumin, ionized serum calcium, 25-hydroxy vitamin D, creatinine, intact PTH, urinary pH) were centrally measured. Serum total calcium (normal, 8.4 to 10.2 mg/dL) and albumin were measured using automated methods. Calcium values were corrected for albumin concentration by the following formula: Alb-Ca = (0.8 [4.0 – patient's albumin] + serum calcium).[12] Ionized serum calcium (normal, 1.12 to 1.32 mmol/L), serum phosphorus, and creatinine were also measured by automated techniques. 25-hydroxy vitamin D was measured by an immunochemiluminometric assay (Abbott Laboratories Diagnostics Division, Abbott Park, IL, USA). Intact PTH (normal, 14 to 72 pg/mL) was measured by an immunochemiluminometric assay (second-generation kit) using the automatic analyzer Modular E170 (Roche Diagnostics, Indianapolis, IN, USA). Estimated GFR was calculated using the modification of diet in renal disease equation. Twenty-four-hour urine collections were obtained at baseline and at 2-week intervals during the 2 months of the study. We calculated the renal clearance of creatinine from 24-hour urinary creatinine and plasma creatinine. We defined hypercalciuria as urinary calcium excretion >4 mg/kg/d. To inhibit the growth of microorganisms in the specimen, boric acid was used as preservative before collection. However, because of the use of acid as preservative, we collected an additional independent urine sample, in the morning, in fasting state, to measure pH. At each visit, we measured volume, sodium, calcium, magnesium, oxalate, citrate, uric acid, potassium, creatinine, urea, chloride, phosphate, cystine, sulphate, and ammonium levels of the 24-hour urine specimen. Relative supersaturation ratios for calcium oxalate, brushite, uric acid, ß struvite, and cystine acid were calculated with the software LITHORISK.[13] The ion activity product of calcium oxalate (AP [CaOx] index) is calculated by means of the following formula:

$$\mathrm{AP(CaOx)\ index} = \frac{\mathrm{A\ (variable)} \times \mathrm{Calcium}^{0.84} \times \mathrm{Oxalate}}{\mathrm{Citrate}^{0.22} \times \mathrm{Magnesium}^{0.12} \times \mathrm{Volume}^{1.03}}$$

The net gastrointestinal alkali absorption was measured by means of Oh's formula.[14]

Outcomes

The primary efficacy outcomes were the difference between the changes in albumin-adjusted serum calcium and the AP(CaOx) index levels observed during the two monthly treatment periods with Ca-Cit or $CaCO_3$, which were centrally assessed. Secondary efficacy outcomes included PCS and MCS (by SF-36 survey), fatigue score, constipation, and adverse events. We defined the optimum clinical range for albumin-adjusted calcium levels between 8 and 9 mg/dL.[3] Changes in albumin-adjusted calcium and AP(CaOx) index levels, as well as on secondary outcomes, were assessed during 2 months after randomization to the treatment groups compared with baseline (time of randomization). We assessed safety by monitoring vital signs, physical examination laboratory tests, and adverse event data, assessed at baseline and at the end of each visit. Adverse events could be reported by patients at any time during the study, including the visits at baseline and the monthly visits up to the end of the study.

Statistical analysis

Sample size calculation

We hypothesized that Ca-Cit does not affect the calcium oxalate supersaturation compared with $CaCO_3$ in HypoPT subjects. Based on the assumption that within-patient standard deviation of the calcium oxalate supersaturation would be 0.5, a total of 24 patients were required to provide an 80% power to detect a difference of 0.43 points in calcium oxalate supersaturation at a two-sided 5% significance level with a probability of type II error of 20%.

To demonstrate that Ca-Cit is as effective as $CaCO_3$ in maintaining serum calcium within the acceptable clinical range, a

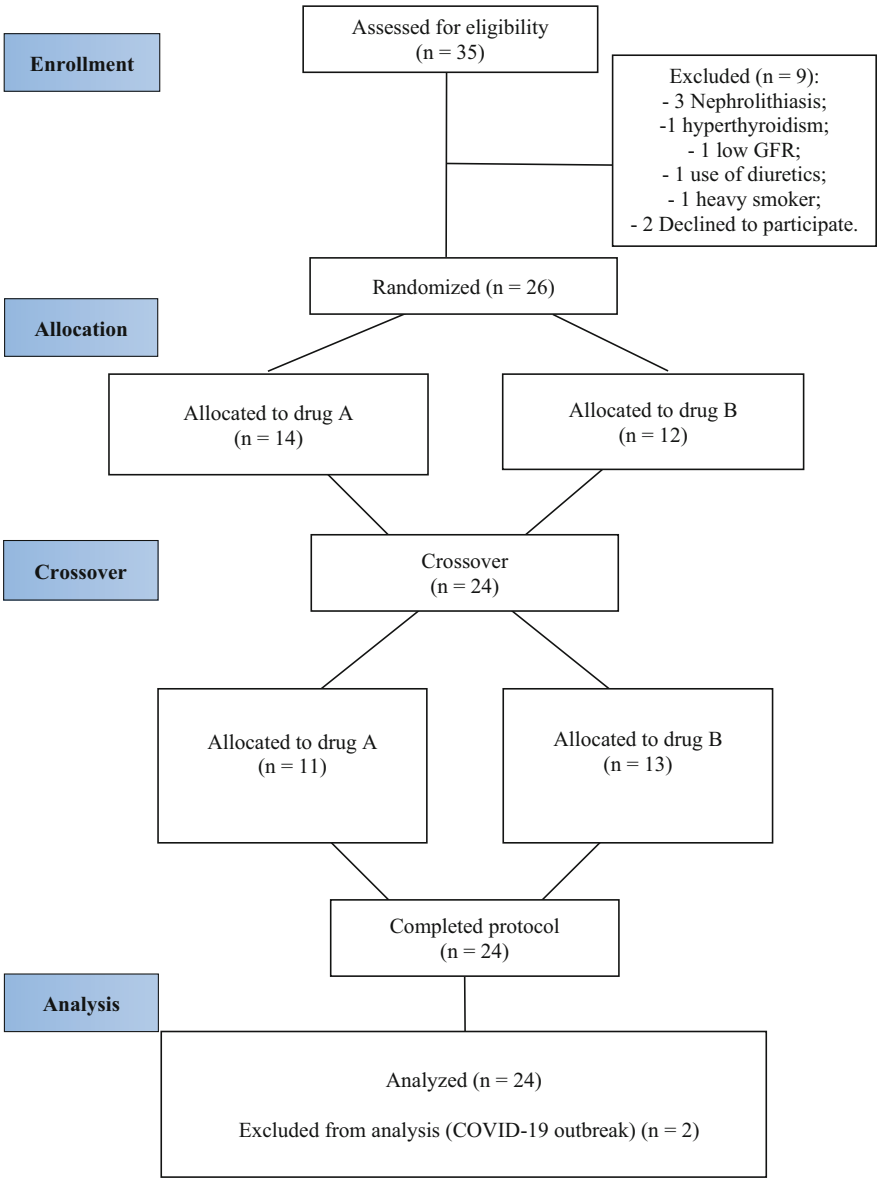

Fig. 1. CONSORT study flow diagram.

sample of 21 people already treated with calcium and vitamin D supplementation would be required. We hypothesized that—at the end of the study period—the mean calcium concentration would not be different from the ideal value (9 mg/dL), accepting a 10% variation as the equivalence limit (ie, accepting as equivalent values between 8.1 and 9.9 mg/dL). Under these assumptions, we would need 11 patients to show equivalence between the two treatments, with an alpha error probability of 5% and a beta error probability of 10%. With the available sample size, we will be able to establish equivalence with an equivalence limit of 0.7 (ie, values between 8.3 and 9.7 mg/dL).

Statistical tests

We evaluated the data distribution using the Kolmogorov–Smirnov test. We analyzed the between-group differences of study variables at baseline by unpaired Student's *t* test after considering whether the subgroups had equal variance using Levene's test. We described the nominal variables as a number and percentage and analyzed them with contingency tables and the Fisher's exact test.

We used several separate 2 × 2 mixed-model analysis of variance (ANOVA) to test the effect of the different calcium supplements on the absolute variation over time (ie, follow-up–baseline levels) of the study variables, with treatment group (Ca-Cit and $CaCO_3$) as between-subjects factor and time (baseline and follow-up) as within-subjects factor. We tested the "group × time" interaction as the hypothesis of interest.

In addition, we compared the relative modifications over time (ie, the percentage of increasing/decreasing between baseline and follow-up: {(follow-up–baseline)/baseline levels} × 100) of study variables when a subject was treated with the different calcium supplements by a paired *t* test.

Table 1. Comparison of Study Population at Baseline When Assigned to Calcium Citrate or Carbonate Supplementation

Variable	Calcium citrate mean (SD)	Calcium carbonate mean (SD)	*p* Value
Body mass index (kg/m^2)	28.95 (5.09)	28.92 (5.06)	0.984
Urinary calcium oxalate supersaturation	4.60 (2.76)	4.09 (2.51)	0.507
Urinary pH	5.85 (0.68)	5.77 (0.81)	0.701
Urinary volume (mL)	2174.62 (1007.53)	2380.00 (524.69)	0.281
Urinary phosphate excretion (mmol/24 h)	16.34 (10.95)	13.53 (8.19)	0.318
Urinary potassium excretion (mEq/24 h)	60.92 (24.97)	52.68 (16.21)	0.183
Urinary sodium excretion (mEq/24 h)	127.18 (78.57)	111.63 (57.31)	0.437
Urinary calcium excretion (mg/24 h)	206.55 (136.72)	196.24 (107.18)	0.772
Urinary calcium/creatinine (24 h) (mg/mg)	0.19 (0.09)	0.18 (0.08)	0.885
Urinary oxalate excretion (mmol/24 h)	0.40 (0.16)	0.36 (0.14)	0.358
Urinary oxalate/creatinine (24 h) (mmol/mol)	42.29 (14.62)	39.21 (13.90)	0.458
Urinary citrate excretion (mmol/24 h)	5.61 (2.88)	5.52 (2.46)	0.912
Urinary citrate/creatinine (24 h) (mol/mol)	0.59 (0.23)	0.59 (0.23)	0.985
Serum calcium (mg/dL)	8.80 (0.56)	8.86 (0.41)	0.704
Serum ionized calcium (mmol/L)	1.10 (0.05)	1.11 (0.06)	0.260
Serum phosphorus (mg/dL)	4.05 (0.63)	4.07 (0.57)	0.905
Serum creatinine (mg/dL)	0.78 (0.17)	0.82 (0.19)	0.430
Serum 25-OH Vitamin D (ng/mL)	27.00 (7.49)	29.00 (9.09)	0.280
Renal clearance of creatinine (24 h) (mL/min)	63.30 (21.39)	61.12 (20.96)	0.402
Net alkali absorption (mEq/d)	32.80 (33.25)	35.20 (28.96)	0.791
Daily dose of calcium supplements (mg)	1171.46 (311.89)	1090.91 (301.51)	0.260
Daily dose of calcitriol (mcg)	0.54 (0.37)	0.48 (0.21)	0.310

We reported the results as means and standard deviation (SD), means and 95% confidence intervals (CI), or mean and standard error (SE), as appropriate.

We used the software IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA) to perform all statistical analyses. For all tests, we set a two-sided alpha level of $p < 0.05$ for statistical significance.

The study was registered with ClinicalTrials.gov ID NCT03425747 on February 8, 2018.

Results

During the study period, we screened 35 consecutive patients with postsurgical chronic HypoPT for eligibility. Nine subjects did not meet the inclusion criteria and were excluded. Fig. 1 shows a summary of patient recruitment and exclusion. Twenty-six patients meeting the eligibility criteria were randomized for the first phase of the crossover trial. After crossover, two participants withdrew from the study due to the COVID-19 outbreak (Fig. 1). Consequently, 24 patients (mean age 54.7 [SD 12.5] years, 21 [87.5%] women) constituted the final study population with a mean PTH value of 15.04 pg/mL (SD 8.68). The dose of active vitamin D at baseline was not different between Ca-Cit and $CaCO_3$ groups (0.54 ± 0.37 versus 0.48 ± 0.21, $p = 0.310$). The prevalence of hypercalciuria in our study population was 33%. No difference in baseline anthropometric characteristics and laboratory biomarkers was found between calcium supplement groups (Table 1).

Biochemical analysis

No difference in terms of AP(CaOx) index was recorded between the two groups. Both absolute variations of serum creatinine, urinary 24-hour oxalate/creatinine ratio, and urinary 24-hour potassium excretion showed a statistically significant group × time interaction in the mixed-model ANOVA. In particular, a reduction of both urinary potassium excretion (−5.66 mEq/24 hours [SD 14.36] versus 5.00 mEq/24 hours [SD 14.90], $p = 0.013$) and oxalate/creatinine ratio (−2.46 mmol/mol [SD 11.93] versus 7.42 mmol/mol (SD 17.63), $p = 029$) was found in association with Ca-Cit supplementation, while the same variable increased in patients treated with $CaCO_3$. No further significant interactions were found for the other measured laboratory biomarkers (Table 2). When we evaluated the change rate of study variables between baseline and 4-week follow-up, the finding was confirmed only for urinary 24-hour oxalate/creatinine ratio (Table 3). No statistically significant difference in the rate of patients with out-of-range serum calcium concentration was detected, neither at baseline (29.2% in Ca-Cit versus 8.3% in $CaCO_3$, $p = 0.137$) nor at the follow-up control.

QOL evaluation

At follow-up, 7 patients (30.4%) treated with $CaCO_3$ supplementation suffered from constipation compared with one (4.3%) receiving Ca-Cit ($p = 0.047$). No difference between groups was found for relative changes in SF-36–PCS score (Ca-Cit: 3.59% [SD 26.44]; $CaCO_3$: 4.90% [SD 35.46]; $p = 0.878$), SF-36–MCS score (Ca-Cit: 6.17% [SD 31.43]; $CaCO_3$: 7.75% [SD 50.67]; $p = 0.904$) and fatigue score (Ca-Cit: −2.60% [SD 33.67]; $CaCO_3$: 36.52% [SD 128.03]; $p = 0.175$).

Discussion

In this prospective double-blind crossover trial, we showed that Ca-Cit is as effective as $CaCO_3$ in maintaining target calcium levels in chronic postsurgical HypoPT. It is believed that Ca-Cit salts, due to their more rapid metabolism and lack of CO_2 production, may increase calcium bioavailability more efficiently and to a greater degree than $CaCO_3$ salts[5] as clearly shown in the setting of bariatric surgery.[15] This reasoning could also lead

Table 2. Comparison of Modifications in Laboratory Tests According to the Type of Calcium Supplementation in the Study Population

Variable	Study arm	Mean baseline (SD)	Mean follow-up (SD)	Mean difference (SD)	Mean difference between groups (95% CI)	*p* Value
Blood tests						
Serum calcium (mg/dL)	Ca citrate	8.80 (0.56)	8.70 (0.41)	−0.11 (0.39)	0.006 (−0.119 to 0.131)	0.336
	Ca carbonate	8.86 (0.41)	8.63 (0.58)	−0.23 (0.40)		
Serum phosphorus (mg/dL)	Ca citrate	4.05 (0.63)	4.04 (0.59)	−0.01 (0.40)	−0.027 (−0.158 to 0.103)	0.924
	Ca carbonate	4.07 (0.57)	4.07 (0.55)	0.00 (0.49)		
Serum creatinine (mg/dL)	Ca citrate	0.78 (0.17)	0.83 (0.19)	0.05 (0.10)	−0.014 (−0.039 to 0.011)	**0.031**
	Ca carbonate	0.82 (0.19)	0.81 (0.18)	−0.01 (0.07)		
Urine tests						
Calcium excretion (mg/24 h)	Ca citrate	206.55 (136.72)	208.63 (127.32)	2.07 (83.42)	9.077 (−13.558 to 31.712)	0.913
	Ca carbonate	196.24 (107.18)	200.79 (131.57)	4.55 (73.01)		
Calcium/creatinine (24 h) (mg/mg)	Ca citrate	0.19 (0.09)	0.19 (0.08)	0.00 (0.08)	−0.008 (−0.042 to 0.027)	0.506
	Ca carbonate	0.18 (0.08)	0.21 (0.16)	0.02 (0.14)		
CaOx supersaturation	Ca citrate	4.60 (2.76)	3.92 (2.16)	−0.68 (3.25)	0.070 (−0.753 to 0.892)	0.287
	Ca carbonate	4.09 (2.51)	4.29 (2.12)	0.20 (2.31)		
Creatinine excretion (g/24 h)	Ca citrate	1.08 (0.42)	1.13 (0.34)	0.05 (0.23)	−0.003 (−0.078 to 0.071)	0.849
	Ca carbonate	1.09 (0.34)	1.12 (0.40)	0.03 (0.27)		
Citrate excretion (mmol/24 h)	Ca citrate	5.61 (2.88)	5.84 (2.82)	0.23 (1.85)	0.068 (−0.534 to 0.670)	0.952
	Ca carbonate	5.52 (2.46)	5.79 (2.96)	0.27 (2.25)		
Citrate/creatinine (24 h) (mol/mol)	Ca citrate	0.59 (0.23)	0.58 (0.21)	−0.01 (0.17)	−0.059 (−0.158 to 0.040)	0.226
	Ca carbonate	0.59 (0.23)	0.70 (0.54)	0.11 (0.45)		
Oxalate excretion (mmol/24 h)	Ca citrate	0.40 (0.16)	0.38 (0.19)	−0.02 (0.16)	0.002 (−0.039 to 0.043)	0.073
	Ca carbonate	0.36 (0.14)	0.42 (0.14)	0.06 (0.11)		
Oxalate/creatinine (24 h) (mmol/mol)	Ca citrate	42.29 (14.62)	39.83 (16.95)	−2.46 (11.93)	−1.854 (−6.254 to 2.546)	**0.029**
	Ca carbonate	39.21 (13.90)	46.62 (16.03)	7.42 (17.63)		
Sodium excretion (mEq/24 h)	Ca citrate	127.18 (78.57)	140.24 (77.80)	13.06 (46.32)	6.416 (−12.711 to 25.543)	0.341
	Ca carbonate	111.63 (57.31)	142.96 (77.63)	31.33 (74.70)		
Potassium excretion (mEq/24 h)	Ca citrate	60.92 (24.97)	55.26 (21.95)	−5.66 (14.36)	2.902 (−1.263 to 7.067)	**0.013**
	Ca carbonate	52.68 (16.21)	57.69 (21.22)	5.00 (14.90)		
Magnesium excretion (mg/24 h)	Ca citrate	85.43 (40.89)	84.66 (34.96)	−0.77 (26.86)	0.778 (−8.877 to 7.322)	0.447
	Ca carbonate	81.56 (30.86)	86.96 (35.16)	5.40 (28.70)		
Phosphate excretion (mmol/24 h)	Ca citrate	16.34 (10.95)	13.66 (8.98)	−2.68 (7.81)	0.781 (−1.560 to 3.123)	0.087
	Ca carbonate	13.53 (8.19)	14.91 (8.54)	1.38 (8.33)		
pH (spot sample)	Ca citrate	5.85 (0.68)	5.96 (0.79)	0.10 (0.75)	0.083 (−0.102 to 0.268)	1.000
	Ca carbonate	5.77 (0.81)	5.88 (0.76)	0.10 (0.49)		
Urine volume (24 hours) (mL)	Ca citrate	2417.50 (972.25)	2450.83 (1089.87)	33.33 (561.22)	−124.792 (−296.925 to 47.342)	0.875
	Ca carbonate	2306.59 (764.21)	2312.50 (818.44)	6.25 (647.11)		
Net alkali absorption (mEq/d)	Ca citrate	32.80 (33.25)	38.10 (30.27)	5.30 (44.19)	−9.628 (−26.643 to 7.387)	0.261
	Ca carbonate	35.20 (28.96)	54.95 (51.73)	19.75 (47.54)		

CI = confidence interval; SD = standard deviation; Ca = calcium; CaOx = calcium oxalate.

to an expectation that Ca-Cit may maintain calcium levels at lower doses than $CaCO_3$. However, the lack of PTH and the mean high dosage of calcium supplementation might have prevented this conclusion to be drawn.

The other endpoint of the study was the evaluation of risk factors for nephrolithiasis assessed by the AP(CaOx) index changes. Although there was a trend toward reduction of AP(CaOx) index in Ca-Cit treated patients, it was not significant. This index is

Table 3. Change Rate (%)[a] of Study Variables Between Baseline and 4-Weeks Follow-up

Variable	Calcium citrate mean (SD)	Calcium carbonate mean (SD)	Mean diff. (SE)	*p* Value
Urine				
Calcium oxalate supersaturation	32.12 (157.28)	16.99 (60.49)	15.14 (39.80)	0.707
Urinary pH	2.32 (12.74)	2.27 (8.54)	0.05 (3.19)	0.986
Urinary phosphate excretion (24 h)	1.65 (63.43)	29.99 (56.76)	−28.34 (18.39)	0.137
Urinary potassium excretion (24 h)	−4.20 (28.43)	12.01 (28.54)	−16.21 (9.90)	0.115
Urinary sodium excretion (24 h)	25.7 (64.9)	38.5 (62.4)	−12.80 (20.00)	0.528
Urinary calcium excretion (24 h)	19.11 (70.05)	7.04 (57.38)	12.08 (22.23)	0.592
Urinary calcium/creatinine (24 h)	13.49 (47.32)	20.76 (79.92)	−7.27 (22.84)	0.753
Urinary oxalate excretion (24 h)	−0.17 (34.34)	22.19 (41.10)	−22.36 (12.89)	0.096
Urinary oxalate/creatinine (24 h)	−4.26 (28.89)	33.10 (64.74)	−37.36 (17.01)	**0.038**
Urinary citrate excretion (24 h)	13.49 (38.42)	7.75 (37.89)	5.74 (13.98)	0.685
Urinary citrate/creatinine (24 h)	11.33 (46.01)	16.20 (55.25)	−4.87 (17.75)	0.786
Blood				
Serum calcium	−1.04 (4.48)	−2.60 (4.58)	1.56 (1.49)	0.307
Serum phosphorus	0.39 (10.00)	0.86 (11.89)	−0.47 (4.01)	0.908
Serum creatinine	6.30 (13.27)	−0.21 (8.20)	6.51 (3.81)	0.101

[a](Follow-up – baseline)/baseline.

particularly important because previous studies have clearly shown higher supersaturation levels for stone formers compared with non-stone formers. Intuitively, higher values of AP(CaOx) index should increase risk of stone formation.[16-19] Many studies focused on potassium citrate (K-Cit) have demonstrated that this salt is able to reduce urinary AP(CaOx) index and hence the risk of nephrolithiasis.[20] In fact, K-Cit is recommended as a first-choice treatment for renal stone disease.[21,22] Although Ca-Cit is a different salt from K-Cit, we expected a similar increase in citrate excretion with a potential effect on urinary AP(CaOx) index. Indeed, Ca-Cit, after rapid metabolism in the stomach, provides an extra alkali load, which in turn may reduce urinary supersaturation with respect to calcium-oxalate (CaOx). However, in our study, the urinary citrate did not differ between Ca-Cit and $CaCO_3$-treated patients. We hypothesized that more citrate remained in the intestine. Indeed, the estimated gastrointestinal alkali absorption[14] was similar in the two groups of patients, with a consequent lack of any urinary pH increase in Ca-Cit-treated patients. Furthermore, PTH is able to modulate the renal distal tubular reabsorption of calcium, whereas in HypoPT subjects, most of the calcium absorbed in the intestine is definitely found in the urine.[1-3,23] The lack of any PTH modulation on tubular calcium reabsorption may have played an additional role in maintaining AP(CaOx) index similar in both treatment arms.

Interestingly, we observed a significant reduction of urinary oxalate excretion in Ca-Cit-treated patients. The reduction of urinary oxalate might be related to the higher gastric solubility of Ca-Cit that made available a greater amount of free calcium ions than $CaCO_3$. These free calcium cations, by forming calcium-oxalate salts in the gastrointestinal tract, may have reduced oxalate intestinal absorption, thus reducing the concentration of oxalate absorbed and thus presented to the renal tubules. This noteworthy observation is relevant to the fact that urinary oxalate is one of the most important promoters of crystal growth,[21,24-26] and the reduction in the excretion of this index might be important in reducing the risk of renal stone formation.[25] Other factors, such as phosphorus, also may promote the nucleation of calcium oxalate monohydrate crystals.[27] Nevertheless, in our study, serum and urinary phosphate levels did not differ between Ca-Cit- and CaCO3-treated patients.

Ca-Cit was also associated with less constipation than $CaCO_3$. It is possible that the residual intestinal citrate forms complexes with magnesium to a greater extent than with $CaCO_3$. These magnesium complexes can have a laxative osmotic action that may explain our finding of an improvement of constipation in Ca-Cit-treated patients.[28] An alternative explanation is that constipation was increased by $CaCO_3$ administration, whose dissolution, by forming CO_2, may be responsible for side effects such as flatulence, general gastrointestinal disorders, and notably, constipation.

However, this is not enough to improve overall QOL in these patients. SF-36 and FACIT are validated but are not disease-specific questionnaires, which may not be sensitive enough for QOL evaluation of HypoPT subjects.[29-32] It is very likely that the high amount of calcium that is necessary to maintain normocalcemia in these patients completely abolished the possible advantages given by Ca-Cit in other categories of patients who generally are prescribed lower doses of calcium. It is also possible that this short-term study was not conducted long enough to see a difference in the QOL parameters.

To our knowledge, this is the first randomized, double-blind, crossover study comparing $CaCO_3$ and Ca-Cit in the treatment of HypoPT. The strengths of the study are both its rigorous design and the choice of a priori primary endpoints (see registration by ClinicalTrials.gov ID NCT03425747). Another important strength is the controlled diet given to the patients, which controlled for many possible confounders on 24-hour urine collections deriving from different food intakes. Finally, only two patients needed a small variation of calcium doses, confirming that all the subjects were on stable therapy before entering the study.

A few limitations of our study should be addressed. First, a carry-over effect has to be taken into account with our study design. However, the nature of the disease required that we could not have an absolute "wash-out" period. However, given the short time-course of oral calcium, the lack of a complete wash-out design probably is unlikely to have affected the results. Second, this was a short study, raising the possibility the longer-term observation might have led to different results. However, the dynamics of the variables being measured in this study are unlikely to require a longer observational period. Third, the

sample size was relatively small but nevertheless substantial given the orphan status of this disease.

However, when we estimated the reduction of AP(CaOx) index, we might have overestimated the effect of Ca-Cit because the lack of PTH seems to mitigate the benefits of citrate in the kidney.

Finally, our findings may not be reflective of other nonsurgical causes of HypoPT or in patients with a history of nephrolithiasis.

Published guidelines on HypoPT recommend Ca-Cit therapy for patients who do not tolerate $CaCO_3$, particularly at a gastrointestinal level.[1-3] This study raises another setting in which Ca-Cit might be preferred, namely those who are at high stone risk.

Further studies on larger groups of HypoPT patients, for perhaps a longer period of time, may help to further document the findings of this study.

Disclosures

All authors state that they have no conflicts of interest.

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Authors' roles: AMN, GT, FV, and AP had the original idea, wrote the study protocol, coordinated the study procedures, and critically revised the report. AMN, GT, AS, DB, GGI, SM, NN, RC, and AP selected, monitored, and cared for patients and collected data. GS did the statistical analysis. AMN, GT, and AP monitored the study. GG advised and followed subjects for the specialized diet during the study period. AMN, GT, JPB, AF, FV, and AP interpreted centralized laboratory measurements. AMN, GT, JPB, AF, PT, GM, FV, and AP analyzed and interpreted data. AMN, GT, JPB, AF, PT, GM, FV, and AP interpreted data and wrote the first draft of the report. All authors revised the first draft and wrote the final version of the manuscript. Open Access Funding provided by Universita Campus Bio-Medico di Roma within the CRUI-CARE Agreement.

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Peer Review

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Data Availability Statement

We will consider sharing de-identified, individual participant–level data that underlie the results reported in this article on receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent to the corresponding author. The corresponding author and lead investigators of this study will discuss all requests and make decisions about whether data sharing is appropriate based on the scientific rigor of the proposal. All applicants will be asked to sign a data access agreement.

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