Supplementary Table 4: Study details and descriptive results of conventional treatment

Study - Design	Population	Intervention	Outcomes of interest	Results	Comments
Canat (2023)[1] - RCT Turkey	Individuals with chronic hypoparathyroidism (67% postsurgical) with a total daily calcium intake (diet and supplementation) < 800 mg (n = 67, 64% female, mean age 52.3±8.8y in study group, 51.2±9.5y in control group)	Study group (n = 32) advised to consume 1000-1200 mg calcium daily Control group (n = 35) advised to continue their diet according to their daily habits	Serum calcium and phosphate levels, 24-h urinary calcium excretion, serum creatinine, eGFR, paresthesia symptoms	After 12 weeks of follow-up: - total calcium level 8.56±0.36 mg/dL in study group vs. 7.67±0.48 mg/dL in controls (p<0.001); 87.5% of study group vs. 8.5% of controls attained target calcium levels (target 8-9.5 mg/dL) - serum phosphate 5.21±0.39 mg/dL in study group vs. 4.9±0.41 mg/dL in control group (p = 0.01) - hypocalcemia requiring emergency admission: none - urinary calcium excretion 229.6±40.1 mg/24h in study group vs. 163.1±38.5 mg/24h in control group (p < 0.001) - serum creatinine 0.79±0.11 mg/dL in study group vs. 0.74±0.11 mg/dL in control group (p = 0.11) - eGFR 98.9±8.7 ml/min per 1.73m^2 in study group vs. 103.3±7.9 ml/min per 1.73m^2 in study group (p = 0.035) - no paresthesia symptoms described	Intervention concerns dietary calcium *Funding: none*
Naciu (2022)[2] - RCT, crossover Italy	Individuals with postsurgical chronic hypoparathyroidism, requiring ≥ 0.25 mcg calcitriol daily and ≥ 1000 mg oral calcium daily (n = 24, 87.5% female, mean age 54.7±12.5 y)	Two phases: phase A (calcium citrate) 1 month, phase B (calcium carbonate) 1 month or vice versa Calcium dose equal to dose before study entry, but titrated during study to optimal range of albumin-adjusted serum calcium between 8 and 9 mg/dL without signs/symptoms of hypocalcemia During study; dietary calcium intake 1200 mg/day and continuing of the same dose of active vitamin D as	Serum calcium level, phosphorus, hypercalciuria, creatinine, gastrointestinal tolerance, QoL	After two months: Mean difference between two groups (95%CI): - serum calcium 0.006 mg/dL (-0.119 to 0.131), p = 0.336 - serum phosphorus -0.027 mg/dL (-0.158 to 0.103), p = 0.924 - serum creatinine -0.014 (-0.039 to 0.011), p = 0.031 - urinary calcium excretion 9.077 (-13.558 to 31.712), p = 0.913 Constipation in 30.4% patients treated with calcium carbonate vs. 4.3% in calcium citrate, p = 0.047 SF-36 and FACIT-Fatigue score: no relative changes in scores between groups	Compares 2 types of calcium preparations Prevalence of hypercalciuria at baseline: 33% *Funding: Biohealth-Italia freely supplied calcium citrate and calcium carbonate tablets*

		before study entry			
Stamm (2022)[3] - Cross-sectional study Germany	Individuals with postsurgical chronic hypoparathyroidism (n = 49, 83.7% female, mean age 57.3±10.5 y)	65% treated with calcium preparations; in 25% in combination with native vitamin D 86% treated with active vitamin D analogues; alfacalcidol in 50%, calcitriol in 33%, alfacalcidol + calcitriol in 2%, dihydrotachysterol in 14% Thiazide diuretics in 17%	Serum calcium and phosphate levels, 24h urinary calcium excretion, QoL	- albumin-adjusted serum calcium mean 2.09 mmol/L (range 1.6-2.39) - serum phosphate mean 1.26 mmol/L (range 0.84-1.75) - urinary calcium excretion mean 5.39 mmol/24h (range 0.49-10.09) No significant differences between the different active vitamin D compounds and biochemical parameters or QoL evaluated by HPQ 28 Calcitriol-related dose-dependent increase on HPQ 28 scales “depression and anxiety” (r_s = 0.64, p = 0.010), “pain and cramps” (r_s = 0.57, p = 0.028), “numbness and tingling” (r_s = 0.58, p = 0.023) and “heart palpitations” (r_s = 0.60, p = 0.017) No dose-dependent effects for alfacalcidol or dihydrotachysterol on any HPQ 28 scale Higher daily calcium intake correlated with HPQ 28 scale “neurovegatative symptoms”, i.e. more complaints of trembling muscles, hot flushes or chills, weakness, dizziness or diarrhea with higher doses of calcium intake (r_s = 0.29, p = 0.044) No significant differences between different doses of native vitamin D and QoL evaluated by HPQ 28	4% on teriparatide Severely underpowered *Funding: none*
Streeten (2017)[4] - Cross-sectional study USA	Individuals with chronic hypoparathyroidism (postsurgical in 70%) using ergocalciferol or calcitriol (n = 30, 77% female, mean age 58.9±16.7y in ergocalciferol group, 50.9±22.6y in calcitriol group)	53% treated with ergocalciferol; mean dose 41326±30198 IU/day “most” were also taking calcium supplements 400-2000 mg/day 47% treated with colecalciferol; mean dose 0.58±0.31 mcg/day; 50% were	Calcium levels, hypocalcemia, hypercalcemia, 24h urinary calcium, creatinine, kidney stones	Ergocalciferol vs. calcitriol: - mean albumin-corrected serum calcium 8.6±0.6 vs. 8.4±0.7 mg/dL, p = 0.37 - 0 patients vs. 4 patients (28.6%) with hospitalization and/or ED visit for hypocalcemia, p = 0.03 - 2 patients (12.5%) vs. 2 patients (14.3%) with hospitalization and/or ED visit for hypercalcemia, p = 1.00 - 24h urinary calcium (measured in 8/16 ergocalciferol patients and 3/14 calcitriol patients): median 171±89 mg/24h vs. 185±183 mg/24h - mean serum creatinine 0.92±0.33 vs. 0.98±0.26 mg/dL, p = 0.71	*Funding: none*

		also taking calcium supplements 250-2000 mg/day		- kidney stone, passed: Yes: 1 vs. 0 patients, p = 0.32 No: 14 vs. 12 patients, p n.r. Unknown: 1 vs. 2 patients - stones or nephrocalcinosis (renal imaging performed in 5/16 patients in ergocalciferol group and 4/14 patients in calcitriol group): 0 vs 0 patients	
95%CI = 95% confidence interval QoL = quality of life, SF-36 = 36-Item Short Form Health Survey FACIT-Fatigue score = Functional Assessment of Chronic Illness Therapy Fatigue Score HPQ 28 = 28-item Hypoparathyroid Patient Questionnaire					

Descriptive results

Quality of Life

Two studies reported on QoL [2, 3]. Naciu *et al*. found no difference in QoL in a cross-over trial of patients using calcium carbonate *vs*. patients using calcium citrate [2], nor did Stamm *et al*. for different preparations of activated vitamin D analogues [3], however; intervention duration was too short/study numbers too small respectively, to draw firm conclusions.

Calcium and phosphate levels

Biochemical control did not differ between calcium carbonate *vs*. calcium citrate [2], or between different preparations of activated vitamin D analogues [3, 4], however; biochemical control did appear to improve with a suitable increase in dietary calcium intake [1]. Again; intervention duration was too short and study numbers too small in these studies to draw firm conclusions.

Chronic kidney disease and renal calcifications

A small study assessing use of ergocalciferol vs. calcitriol (*n* = 30, where renal imaging was performed in 9) found no kidney stones or nephrocalcinosis [4].

Cramps, tetany, seizures, and neuropsychological endpoints

Paresthesia were reported by none of the patients in the RCT assessing effects of adding extra dietary calcium [1].

Gastrointestinal symptoms

There were no differences in gastrointestinal outcomes between the different activated vitamin D analogues, nor a dose-dependent effect [3]. However, a better gastrointestinal tolerance for calcium citrate than for calcium carbonate was reported [2].

Pain (bone, muscle, and nerves)

A small study (*n* = 49) assessing the influence of various activated vitamin D analogues on the 28-Item Hypoparathyroid Patient Questionnaire (HPQ 28), and reported no significant differences between the different activated vitamin D analogues, nor a dose-dependent effect for alfacalcidol or dihydrotachysterol, but a calcitriol-related dose-dependent increase was reported on the HPQ 28 scale "pain and cramps" ($r_s = 0.57$, $p = 0.028$) [3].

Other outcomes

No studies reported on mortality, cardiovascular disease, disability or sick leave, pill burden, bone markers, fractures or BMD, increased susceptibility to infection, or cataract.

References

1. Canat, M.M., et al., *The effects of adequate dietary calcium intake in patients with hypoparathyroidism non-adherent to treatment: a prospective randomized controlled trial.* Rev Assoc Med Bras (1992), 2023. **69**(11): p. e20230406.
2. Naciu, A.M., et al., *Calcium Citrate Versus Calcium Carbonate in the Management of Chronic Hypoparathyroidism: A Randomized, Double-Blind, Crossover Clinical Trial.* J Bone Miner Res, 2022. **37**(7): p. 1251-1259.
3. Stamm, B., et al., *The Influence of Conventional Treatment on Symptoms and Complaints in Patients With Chronic Postsurgical Hypoparathyroidism.* JBMR Plus, 2022. **6**(2): p. e10586.
4. Streeten, E.A., et al., *Hypoparathyroidism: Less Severe Hypocalcemia With Treatment With Vitamin D2 Compared With Calcitriol.* J Clin Endocrinol Metab, 2017. **102**(5): p. 1505-1510.