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Is calcium supplementation always needed in patients with hypoparathyroidism?

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Summary

Oral calcium salts are recommended for the treatment of chronic hypoparathyroidism (HypoPT), although dosimetry is variable between individual patients and clinicians. However, patient feedback on calcium salts can be negative, particularly due to gastrointestinal side effects and hypercalciuria-related complications. We begin with a clinical case of a HypoPT patient taking oral calcium salts following thyroid surgery, who requested support in reducing her dose of these with a view to stopping entirely. To evaluate her request, we first describe the usual treatment of HypoPT according to current guidance and then present data from (a) a case note review of a cohort of 24 HypoPT patients managed with a "no calcium" treatment regimen by single physician (b) a comprehensive online survey of HypoPT patients' treatment and experiences (n = 330). The case note review found that target range serum calcium levels were successfully achieved in all 24 patients since transitioning to a "no calcium" regimen, without any breakthrough hypocalcaemia-related symptoms, the development of new renal stones, the occurrence of calcium-related hospital admissions or the finding of significant hypercalciuria. The online survey identified 36% of HypoPT patients who continued to take activated vitamin D, but had discontinued calcium supplements. HypoPT patients not currently taking calcium reported a significantly lower prevalence of adverse effects and outcomes, both compared with their previous experiences whilst taking calcium and also compared with the 64% of patients who continued to take oral calcium. We conclude that, subject to methodological limitations, there are significant issues of tolerability arising from conventional calcium-based treatment regimens for patients with chronic HypoPT. For selected patients, it may be reasonable to facilitate a managed therapeutic transition to "no calcium" regimen, and we also propose that calcium-based regimes be prospectively evaluated against calcium-free (or calcium-low) alternatives.

KEYWORDS
Calcium, dyspepsia, hospitalization, Hypoparathyroidism, patient survey, vitamin D

1 | INTRODUCTION

Hypoparathyroidism (HypoPT) is a rare endocrinopathy characterized by hypocalcaemia, with low or "inappropriately normal" serum levels of parathyroid hormone (PTH). It is estimated to affect 60 000 to 115 000 individuals in the United States.[1] Although sometimes congenital, it mostly occurs as a sequela of neck surgery, especially total thyroidectomy, where it can be transient or permanent.[2]

Lifelong treatment of chronic HypoPT targets the avoidance of symptomatic hypocalcaemia, whilst avoiding biochemical hypercalcaemia and minimizing hypercalciuria-associated deterioration in kidney function.[1]

1.1 | What therapies are currently recommended for the treatment of chronic HypoPT?

All major guidelines recommend lifelong therapy with oral calcium and activated vitamin D (calcitriol or alfacalcidol); treatment of concomitant hypovitaminosis D with unhydroxylated D3 (colecalciferol) or D2 (ergocalciferol) is also recommended.[1,2] Thiazide diuretics also have a potential role in managing HypoPT (and non-HypoPT)-related hypercalciuria, given their effect to reduce urinary calcium excretion. However, their effectiveness in HypoPT has only been confirmed for patients adhering to dietary salt restriction and taking higher thiazide doses than those typically prescribed in the UK for the treatment of hypertension.[3]

Until recently, HypoPT was the only hormonal disorder where treatment did not involve replacing the missing hormone. However, based upon a study showing its ability to achieve stabilization of serum calcium concentrations and reduce the daily calcium and active vitamin D needed up to 50%,[4] the European Medicines Agency granted marketing authorization for full-length recombinant human parathyroid hormone Natpar® (rhPTH[1-84]) in adult patients with chronic HypoPT as an adjunctive, rather than sole therapy, and only for patients who meet certain criteria.[1] Nevertheless, in view of rhPTH drug cost and reimbursement issues, guidelines from major scientific societies continue to emphasize the centrality of oral calcium supplements to the treatment of chronic HypoPT[1,2]; albeit that European physicians seem to prescribe lower calcium doses than their North American colleagues.

1.2 | What are the particular challenges in managing patients with chronic HypoPT?

In HypoPT, the lack of PTH-mediated renal tubular calcium reabsorption necessarily predisposes to hypercalciuria when taking calcium or activated vitamin D supplements. Chronic hypercalciuria, in turn, predisposes patients to nephrocalcinosis, kidney stones, renal impairment or even death.[5,6] Thus, achieving this balance can be challenging even in expert hands.

We discuss a clinical case highlighting the narrative of a HypoPT patient taking oral calcium salts following thyroid surgery, who was later successfully transitioned to a calcium-free regimen. We follow this by presenting the results of a chart review data from 24 patients under our care who had also transitioned to a "no calcium" treatment regimen. Finally, we present data and analysis from the very first, comprehensive online survey of a large cohort (n = 330) of HypoPT patients—all of whom had originally received oral calcium salts—exploring their experiences whilst taking (or not taking) oral calcium.

2 | CLINICAL CASE

2.1 | Clinical features and presentation

A 56-year-old woman with a 10-year history of chronic hypoparathyroidism (HypoPT) following total thyroidectomy for thyrotoxic Graves' disease requested a referral to our endocrine service, citing difficulties adhering to her calcium-based treatment regimen and enquiring about alternative treatment strategies that might enable her to take less oral calcium or preferably none at all.

She had developed symptomatic and persistent postoperative hypocalcaemia and was started on oral calcium salts (Calcium carbonate with calcium lactate gluconate–Sandocal®) at a dose of 1 g three times daily; later reduced to twice daily with the further addition of Alfacalcidol 0.75 µg twice daily. She experienced severe gastrointestinal side effects, with gastroscopy-proven reflux oesophagitis and gastritis—requiring long-term treatment with proton-pump inhibitor (Lansoprazole 30 mg)—that in turn resulted in hypomagnesaemia (0.4-0.6 mmol/L). Oral magnesium replacement was poorly tolerated due to diarrhoea, and she had been admitted to hospital on three occasions over five years—twice with symptomatic hypocalcaemia and hypomagnesaemia, and once with hypercalcaemia and biochemical dehydration.

Medical history also included hypertension, anxiety and depression. Body mass index was 29 kg/m^2 (weight 80 kg, height 1.65 m) and blood pressure 155/86 mm Hg. Other medication comprised levothyroxine 125 mcg, amlodipine 5 mg and citalopram 10 mg daily, along with loperamide 2 mg when required.

2.2 | Investigations

Biochemical evaluation varied according to her level of adherence to calcium and magnesium supplements, with serum-adjusted calcium 2.0-2.3 mmol/L [reference range 2.20-2.60], ionized calcium 1.05-1.22 mmol/L [1.19-1.37 mmol/L]); magnesium 0.5-0.6 mmol/L [0.7-1.0]; phosphate 0.7-1.0 mmol/L [0.80-1.50]; serum 25(OH)D$_3$ 38 nmol/L (autumnal); urine calcium/creatinine ratio 0.85-1.2 µmol/mol [<0.70]. No stones or nephrolithiasis were visualized on renal sonography.

2.3 | Management

She was commenced on colecalciferol 1,600 IU daily and ranitidine 300 mg twice daily, and advised to restrict lansoprazole to "as required use"; amlodipine was replaced with Indapamide MR 1.25 mg daily. She was advised to try reducing Sandocal 1g from a whole to a half tablet twice daily 2 weeks into the new drug regimen.

Two months later, repeat biochemistry showed 25(OH)D$_3$ 65 nmol/L, adjusted calcium 2.15 mmol/L, magnesium 0.7 mmol/L and urine calcium/creatinine ratio 0.4 µnmol/mol. Blood pressure was 146/78 mm Hg. The patient confirmed near-resolution of gastro-oesophageal reflux symptoms and, although we had planned a more gradual transition towards her desired "no calcium" regimen,

she admitted to not having taken any lansoprazole, magnesium, sandocal or indeed ranitidine for the previous two to three weeks.

3 | CHART REVIEW OF A LOCAL "NO CALCIUM" TREATMENT PROTOCOL

We conducted a local records-based survey, examining clinical and biochemical outcomes of a local "no calcium" treatment protocol for managing patients with chronic HypoPT and comparing these with recommended outcome standards. This approach was adopted by a single endocrinologist (RQ) since January 2005, prompted initially by requests from several patients.

3.1 | Principles of the "no calcium" protocol

Patients previously taking oral calcium to maintain their biochemistry within the target range are given the option of transitioning to a "no calcium" treatment protocol, whose principals are discussed and agreed with them in advance, comprising:

- Maintain serum 25OHD concentrations greater than 75 nmol/L, so as to remove any conceivable effect of seasonal hypovitaminosis D on calcium homeostasis.
- Use the lowest effective dose of Alfacalcidol to achieve low-normal serum corrected and ionized calcium levels, whilst aiming to maintain urine calcium/creatinine ratio within the local reference range.
- In patients requiring blood pressure control, we use low-dose thiazide diuretic as monotherapy or in combination with other antihypertensives.
- Dyspeptic symptoms permitting, we eschew proton-pump inhibitors (PPI) in favour of H_2 blockers for any patient with a documented episode of hypomagnesaemia.

- HypoPT patients transferred to our service, having previously been started on calcium supplements by their surgeon or other physicians, undergo progressive down-titration of calcium dose, with adjustment of other factors, until complete elimination is achieved.

3.2 | Patient data

Twenty seven patients with chronic postsurgical HypoPT, all but one UK Caucasian, are currently under the care of a single endocrinologist (RQ); of whom, 24 have been fully transitioned to a "no calcium" regimen (Table 1), with the remaining three being relatively "new entrants," still being actively transitioned and thus excluded from further analysis. The median age at evaluation was 63 years (range 28-85), and 83% of patients (n = 21) were females. The median time after surgery was 17.8 years (range 2-59). 54% (n = 13) were on low-dose thiazide diuretics (Bendroflumethiazide 0.625-2.5 mg or Indapamide MR 1.5 mg, daily)—not far off the prevalence of hypertension in patients aged 60+ in the UK.[7] Higher doses of thiazides and explicit dietary salt restriction were not employed.[2,5]

Whilst taking oral calcium supplements prior to transitioning to their new regimen, one patient experienced recurrent kidney stones and two others experienced calcium-related hospital admissions. On the no calcium regimen, target range serum calcium levels were achieved without significant hypercalciuria (Table 1). Crucially, no patients experienced any calcium-related hospital admissions or renal stones since transitioning to the "no calcium" regimen, and all remained consistently free of hypocalcaemia-related symptoms.

In one patient, it had proved particularly difficult to maintain eucalcaemia, despite close monitoring and active management of her alfacalcidol dose. She had been admitted with alternating hypercalcaemic dehydration and hypocalcaemic symptoms at least

TABLE 1 Data on cohort of 24 chronic HypoPT patients treated without oral calcium

Parameter	Normal range/Units	Mean	SD	Min	Max	Median	Interquartile range
Adjusted Ca	2.20-2.60 mmol/L	2.2693	0.08853	2.13	2.44	2.2800	0.15
i.Ca	1.19-1.37 mmol/L	1.0864	0.05891	0.95	1.21	1.0950	0.05
Phosphate	0.80-1.50 mmol/L	1.3043	0.17973	0.99	1.58	1.2800	0.26
Magnesium	0.7-1.0 mmol/L	0.7786	0.13178	0.54	0.96	0.8050	0.27
ALP[a]	30-130 U/L	92.6429	50.67181	33.00	239.00	80.5000	55.75
Creatinine	umol/L	91.2143	24.90344	60.00	133.00	85.0000	46.25
eGFR	mL/min/1.73m^2	65.1429	18.78976	34.00	91.00	68.0000	31.25
uCCR[a]	<0.70 mol/umol	0.3936	0.39884	0.13	1.64	0.2700	0.28
25OHD	nmol/L	118.0000	25.12431	78.00	156.00	118.0000	47.25
PTH	1.1-6.4 pmol/L	1.7857	0.83928	0.60	3.20	1.6000	1.28
D3 dose[a]	IU/day	1422.428	778.49240	800.00	2857.00	1100.000	1000.00
1Alpha dose[a]	µg/day	1.1796	0.65168	0.25	3.00	1.1325	0.63

GFR, Glomerular filtration rate; uCCR, urinary calcium creatinine ratio; 25OHD, 25, hydroxy vitamin D; PTH, parathyroid hormone.
[a]Using the Shapiro-Wilk test for normality, all data were normally so mean with standard deviation should be expressed, for ALP, uCCR, D3 and 1Alpha where median ± interquartile range is shown.

twice each year over the 6 years since laryngectomy (with adjuvant radiotherapy and cisplatin-based chemotherapy). Due to history of gout (on long-term allopurinol prophylaxis) and postcisplatin hypomagnesaemia (on long-term replacement), we were initially reluctant to prescribe thiazide diuretics for hypertension. However, in the 18 months since commencing ultra-low-dose Bendroflumethiazide (2.5 mg: ½ tablet taken on alternate days), her calcaemic control uric acid level and renal function have remained consistently within tolerances.

4 | SURVEY OF HYPOPARA UK MEMBERS

4.1 | Principles underpinning the survey

We commissioned a web-based online survey in which patients suffering from HypoPT were asked about their current and past replacement regimens—in relation to calcium salts, unhydroxylated (ergocalciferol D2 and/or colecalciferol D3) and activated (calcitriol or alfacalcidol) vitamin D—and their experiences of adverse effects (Appendix S1). The survey was created via survey monkey website (https://www.surveymonkey.com/) with subscription upgraded to allow more than 100 responses. The survey went live for 10 days (17 to 27 August 2018) and was closed after achieving a predefined target of 300+ responses. It was distributed as a web link to the 1500 members of the patient support group (Hypopara UK) through personal emails and social media groups. HypoPara UK predominantly comprises UK residents, but also many non-UK European Anglophones. Data analysis was undertaken using the Statistical Package for the Social Science (SPSS version 21). Data were expressed as count and percentages. The analysis was performed using z test to compare proportions. The P value of < 0.05 was considered as significant.

4.2 | Patient survey data

Three hundred and Thirty members of Hypopara UK in the United Kingdom and Europe completed the survey (22% of all members). The majority of responders were treated for HypoPT for the previous 1-5 years (32.12%, n = 106); 6.36% (n = 21) for less than 1 year; 24.24% (n = 80) for the previous 5-10 years; 23.33% (n = 77) for 10 to 20 years and 13.94% (n = 46) had received treatment for over 20 years. All responders (100%; n = 330) had initially received oral calcium and the majority (64%, n = 208) continued to do so regularly, but 36% had since discontinued calcium, either on their own initiative (14.46%, n = 47) or on the advice of their physician (21.54%, n = 70). 86.81% (n = 283) of responders (including 100% of those not taking oral calcium) were taking calcitriol or alfacalcidol), but only 44.85% (n = 148) were taking any unhydroxylated vitamin D.

Whilst taking calcium salts, patients were more likely to suffer from constipation (n = 112/292, P < 0.005) and troublesome dyspepsia symptoms (n = 161/292, P < 0.005), requiring concomitant treatment with regular laxatives (n = 40/372, P = 0.127) and/or regular antacids (eg proton-pump inhibitors and H_2 receptor blockers) (n = 72/329, P = 0.012). Current regular daily calcium intake was significantly associated with the development of kidney stones (n = 36/292, P = 0.003) and with hospitalization due to either hypercalcaemia (n = 33/292, P < 0.005) or hypocalcaemia (n = 122/292, P < 0.005) (Figure 1).

5 | DISCUSSION

5.1 | What is the role of unhydroxylated vitamin D for UK patients with chronic HypoPT?

In patients with HypoPT, one component of the pathophysiology of chronic hypocalcaemia is the lack of PTH-mediated activation of 25OHD in the kidneys, underpinning the use of an activated form of vitamin D in long-term disease management. Moreover, there is a relatively high population prevalence of hypovitaminosis D in the UK; at the spring equinox, 50, 35 and 16% of 45-year-old Caucasians had 25OHD levels below 50, 40 and 20 nmol/L, respectively.[8] Over the past 20 years, there has also been a steep rise in the reported hospitalizations due to rickets in England (one of the southernmost nations forming the UK), currently standing at around 6 cases per 100 000 children/year.[9] Accordingly, guidance from SACN (UK
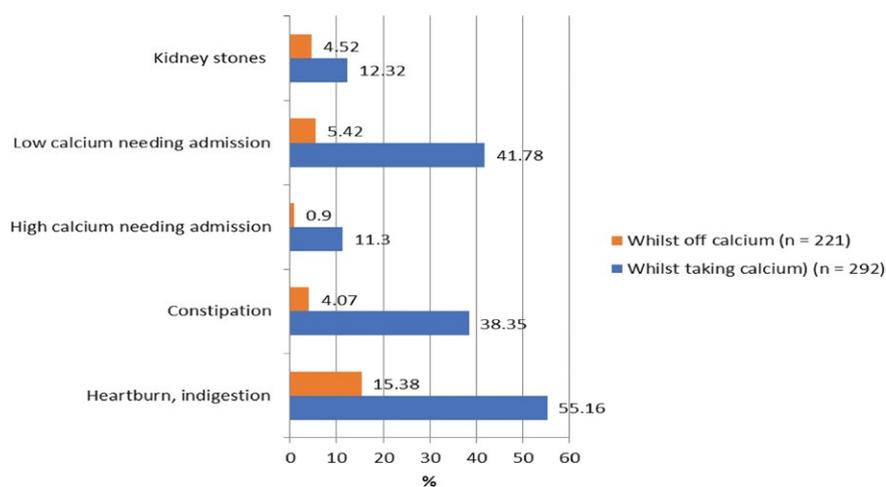
FIGURE 1 Adverse effects and complications of daily calcium intake in patients with HypoPT [Colour figure can be viewed at wileyonlinelibrary.com]

Scientific Advisory Committee on Nutrition) recommends a universal daily oral intake of 10μg (400 IU) unhydroxylated D2 or D3 for the general population aged 1 year or older),[10] Given that, according to our survey, only a minority of HypoPT patients are currently receiving any unhydroxylated vitamin D, this might lead to a greater requirement for calcium or activated vitamin D (calcitriol or alfacalcidol).

The optimum level of 25OHD in the general population remains to be conclusively defined and whether the same values should apply to symptomatic patients with defined disorders of bone mineral metabolism is likewise unclear. Nevertheless, for HypoPT patients, targeting serum 25OHD greater than 50 nmol/L is generally recommended.[1,2] Patients in our cohort received a mean daily dose of 1,400 IU colecalciferol, so as to achieve 25OHD levels greater than 75 nmol/L. Our intention in adopting this higher threshold was to remove any possible element of seasonal hypovitaminosis D.

Patients with HypoPT may accrue additional benefits from unhydroxylated vitamin D. With its much longer half-life, it potentially offers improved stability of calcium haemostasis and lower risk of hypercalcaemia compared with activated vitamin D and oral calcium salts.[11] Moreover, at high concentrations, even unhydroxylated vitamin D can activate vitamin D receptors and undergo PTH-independent hydroxylation in extrarenal tissues.[12] Finally, unhydroxylated vitamin D might also be metabolized to unknown analogues that could benefit "off-target" effects.[11]

5.2 | What is the role of oral calcium salts in UK patients with chronic HypoPT?

In patients with HypoPT, maintaining an adequate daily calcium intake from dietary sources (with oral supplementation if necessary) is obviously advisable, and an elemental calcium intake of 800-2000 mg daily is recommended for the general population.[2] Hence, oral calcium salts are typically prescribed for patients with HypoPT, albeit at variable doses—up to 9 g daily in some patients.[13] In a recent members' survey by HypoPara UK, 41.5% of reported a daily calcium dose greater than 2g, with five individuals (2.6%) taking 10g or more daily (Appendix S2). This was surprising, because although dietary preferences and ethnicity can strongly impact on calcium intake—which can be estimated using simple questionnaires[14]—aggressive supplementation beyond this is a recognized risk factor for the development of hypercalciuria and nephrocalcinosis.[15,16] Moreover, taking more than 500 mg of calcium in single ingestion exceeds the maximum absorptive capacity of the intestine[17,18] and will add no benefit; merely predisposing to more adverse effects.

Our survey indicates that, for many patients with chronic HypoPT, calcium supplements are unpopular and associated with adverse effects, leading more than a third them to discontinue calcium supplements—with or without the agreement of their physician. HypoPT patients not currently taking calcium reported a significantly lower prevalence of adverse effects and outcomes, both compared with their previous experiences whilst taking calcium and also compared with the 64% of patients who continued to take oral calcium. To counteract the undesirable effects of oral calcium, 21.8% (n = 72/329) of responders needed to co-administer regular antacid drugs. This is an important observation because a state of achlorhydria (resulting from the use of the more powerful antacids) will reduce gastric absorption of calcium, thereby potentially necessitating higher doses of elemental calcium to maintain eucalcaemia.[19]

In our survey, the use of oral calcium was associated with an increased chance of hospitalization, both due to hyper- and hypocalcaemia. The mechanism of hypercalcaemia is readily conceptualized, but the association of calcium intake with hypocalcaemic admissions appears counterintuitive. However, it may be that HypoPT patients with untreated hypovitaminosis D, or receiving inadequate doses of calcitriol or alfacalcidol, may compensate most of the time by taking a higher dose of calcium salts, but are then predisposed to develop hypocalcaemia whenever they reduce or stop calcium salts due to adverse gastrointestinal effects.

Although our survey data provide the first detailed "snapshot" of the experience of patients with chronic HypoPT, there are key limitations. Participants were self-selected, meaning that we could not objectively verify their diagnosis of HypoPT. Moreover, there is a recognized tendency for patients with the more severe, complex or problematic disease to become active members of patient support groups and thus potentially bias survey data. Finally, those patients who had been able to wean themselves off oral calcium salts may have had milder disease than those who had not done so (or were unable to do so).

6 | CONCLUSIONS

Provided that confounding factors such as hypovitaminosis D and PPI-induced hypomagnesaemia are rigorously eliminated, it is feasible to consider a "no calcium" regimen in selected HypoPT patients experiencing adverse effects from calcium supplements. This regimen might not fit all HypoPT patients, especially those with dietary calcium deficiency, or with difficult-to-treat hypocalcaemia, where weaning oral calcium might be problematic. However, a no calcium (or lower calcium) approach could be considered for those suffering major side effects or complications directly attributed to ingested calcium. For the future, this approach warrants comparison with standard "calcium-heavy" regimens as part of a larger prospective trial comparing long-term outcomes and tolerability.

DISCLOSURES

The authors reported no conflicts of interest.

DATA SHARING STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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