


## ORIGINAL ARTICLE

# UK national chronic hypoparathyroidism audit

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## Abstract

**Objectives:** Individuals with chronic hypoparathyroidism may experience suboptimal medical care with high frequency of unplanned hospitalisation and iatrogenic harm. In 2015 the European Society for Endocrinology published consensus guidelines on the management of chronic hypoparathyroidism. We set out to audit compliance with these guidelines.

**Methods:** Using these recommendations as audit standards we worked with the Society for Endocrinology and Parathyroid UK to conduct a national audit of management of chronic hypoparathyroidism in the United Kingdom. Endocrine leads in 117 endocrine departments were invited to participate in the survey by completing a data collection tool on up to 5 sequential cases of chronic hypoparathyroidism seen in their outpatient clinics in the preceding 12 months. Data were collected on 4 treatment standards and 9 monitoring standards. Data on hospitalisations and Quality of Life monitoring were also collected.

**Results:** Responses were received from 22 departments giving a response rate of 19%, concerning 80 individual cases. The mean age of subjects was 48.4 years. The main findings were that the commonest cause of hypoparathyroidism was post surgical (66.3%). Treatments taken by the group included activated vitamin D analogues (96.3%), oral calcium salts (66.3%), vitamin D supplements (17.5%), thiazide diuretics (5%) and rhPTH<sub>1-34</sub> (1.3%). Compliance with the audit standards varied between 98.8% and 60% for the treatment standards and between 91.3% and 20% for the monitoring standards. Some of the areas of weakness revealed include low rates of 24 h urinary calcium excretion monitoring, serum magnesium monitoring and low rates of renal imaging where indicated. In addition and importantly, 16.3% of subjects had experienced at least one hospital admission in the preceding 12 months.

**Conclusion:** We conclude that further improvements in the UK national standard of management of chronic hypoparathyroidism should be made and that this will benefit both quality of life, morbidity and potentially mortality in this group of patients.

## KEYWORDS

calcium, conditions, hypocalcemia, hypoparathyroidism, parathyroid

List of contributing clinicians is available as Supplementary Information Appendix S2.

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## 1 | INTRODUCTION

Chronic hypoparathyroidism is a rare disease with a prevalence of 37 per 100,000.<sup>1,2</sup> It usually arises due to operative trauma to the parathyroid glands during thyroidectomy or other anterior neck surgery although a range of other causes are also seen including autoimmune, genetic, mineral deposition disorders and others.<sup>1,3</sup> Acute hypoparathyroidism is conventionally defined as that which lasts less than 6 months after surgery and is terminated by spontaneous recovery of parathyroid function and chronic hypoparathyroidism is that lasting longer than 6 months and which rarely recovers. The major clinical manifestations of chronic hypoparathyroidism relate to hypocalcaemia and include tetany, paraesthesia, carpopedal spasm and muscular cramps. Other symptoms include impaired cognition, neuropsychological manifestations and reduced quality of life. Clinical manifestations may also arise due to complications of treatment, especially where this is insufficiently or ineptly monitored and managed and may include the occurrence of nephrocalcinosis, nephrolithiasis and impairment of renal function.<sup>4</sup> Unlike management of other endocrine deficiency states where treatment with hormone replacement therapy is the norm, individuals with chronic hypoparathyroidism are conventionally managed with activated vitamin D compounds in the form of alfacalcidol or calcitriol and oral calcium salts including calcium carbonate and others.<sup>4</sup> The main risks of these treatments arise from insufficient biochemical monitoring and include symptomatic hypocalcaemia, iatrogenic hypercalcaemia and renal manifestations as described above. Treatment with recombinant human parathyroid hormone as hormone replacement therapy is now licensed in some areas of the world although the field is very much at the dawn of this era and there are still shortcomings and limitations of this treatment in its current form and further development is still required.<sup>5</sup> Individuals with chronic hypoparathyroidism may experience suboptimal care with a high frequency of unplanned hospitalisation<sup>6</sup> and occurrence of iatrogenic harm.<sup>7</sup> In 2015 the European Society for Endocrinology published authoritative, evidence base consensus guidelines on the management of chronic hypoparathyroidism.<sup>8</sup> Since this time other consensus guidelines on the management of chronic hypoparathyroidism have also been published. Specifically, these are: a summary statement and guideline from Brandi and colleagues in 2016<sup>9</sup> and a Canadian and international consensus paper by Khan et al.<sup>10</sup> in 2019. The main difference between these three documents reflects the accumulating evidence base supporting the use of rhPTH1-84 in that Bollerslev et al.<sup>8</sup> recommend against its use where as Brandi et al.<sup>9</sup> and Khan et al.<sup>10</sup> promote its use under specific circumstances and both documents provide specific evidence based recommendations for when to consider its use. Other differences between the documents are that Brandi et al.<sup>9</sup> suggest the use of phosphate binders when needed and also propose key objectives for a future research agenda in the management of hypoparathyroidism and Khan et al.<sup>10</sup> include a very useful section on the management of hypoparathyroidism in pregnancy and a detailed section summarising the evidence base around complications of treatment.

Using the consensus management recommendations from the 2015 European Society for Endocrinology document<sup>8</sup> as audit standards we worked with the Society for Endocrinology and the patient support group Parathyroid UK to conduct a UK national audit of management of chronic hypoparathyroidism during the second half of 2020. We used these recommendations as they are the most specific and proscriptive of the three sets of guidelines, especially around monitoring frequencies, and therefore lent themselves most readily to forming a set of audit standards.

## 2 | METHODS

Endocrine leads in 117 endocrine departments in the United Kingdom were invited to complete a survey of up to 5 sequential cases of chronic hypoparathyroidism seen in their department's outpatient clinics in the preceding 6 months. The data collection tool and audit standards were developed from the recommendations in the European Society for Endocrinology Chronic Hypoparathyroidism management guideline.<sup>8</sup> Specifically, the audit standards employed were:

- Treatment standards: (1) Recommend treatment of all patients with chronic hypoparathyroidism with an albumin adjusted serum calcium level <2.0 mmol/L; (2) Recommend the use of activated vitamin D analogues plus calcium supplements in divided doses as the primary therapy; (3) Recommend against the routine use of replacement therapy with PTH or PTH analogues; (4) Recommend vitamin D supplementation in a daily dose of 400–800 IU to patients treated with activated vitamin D analogues.
- Monitoring standards: (5) Recommend routine biochemical monitoring of albumin adjusted serum calcium (e.g., every 3–6 months); (6) Recommend routine biochemical monitoring of serum phosphate (e.g., every 3–6 months); (7) Recommend routine biochemical monitoring of serum magnesium (e.g., every 3–6 months); (8) Recommend routine biochemical monitoring of creatinine (e.g., every 3–6 months); (9) Recommend routine monitoring of estimated Glomerular Filtration Rate (eGFR) (e.g., every 3–6 months); (10) Recommend routine assessment of symptoms of hypocalcaemia and hypercalcaemia at regular time intervals (e.g., every 3–6 months); (11) Suggest considering monitoring of 24 h urinary calcium excretion at regular intervals (1–2 yearly); (12) Recommend renal imaging if a patient has symptoms of renal stone disease or if serum creatinine levels start to rise; (13) Advise against routine monitoring of bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) scans.

In addition, as recommended in the European Society for Endocrinology chronic hypoparathyroidism management guidelines, we also collected data on: Hospitalisations in the preceding 12-month period and the monitoring of Quality of Life scores as standards 14 and 15, respectively.

The data collection data tool was made available both as a "Survey Monkey" online form (Figure S1) accessed via a link in an email and as a word document (Appendix S1) attached to the invitation email that could be completed and saved and returned by email or printed, completed in hard copy and mailed back to the investigators.

A list of names and institutional email addresses of department leads was compiled from personal contacts, web searches and with help from the Society for Endocrinology. All communications from the research team to departmental leads were via email. An initial email invitation was sent and this was followed at approximately monthly intervals by two reminder emails. In addition, the survey was promoted via the Society for Endocrinology clinicians' newsletter, via the society's Bone and Mineral Network and via direct email contact to clinician members of Parathyroid UK with assistance of the Parathyroid UK offices. The first email invitations were sent in June, 2020 and a deadline of 1st October 2020 was used for cut off of data returns.

The authors' own department did not make a data return to avoid any risk of biasing the data. All results were collated in Microsoft Excel (Excel 365) and statistical analysis performed in SPSS (SPSS v 26.0 IBM).

### 3 | RESULTS

Useable data was available from 80 individual data returns (49 via online returns and 31 via word doc proformas) covering the care of 80 unique UK patients with chronic hypoparathyroidism during a 12-month survey period from a date 12 months before the date of the first return in 2020. These 80 returns originated from 22 separate endocrinology departments from across the United Kingdom including 5 from Northern Ireland and 75 from departments in England. This equated to a response rate of 19% (invitations had been sent to 117 departments and were received from 22).

The mean age of the 80 subjects was 48.4 years. Causes of hypoparathyroidism were reported as: post surgical, 53 (66.3%); genetic 10 (12.5%); idiopathic 8 (10%); autoimmune 6 (7.5%); post-radiation 1 (1.3%) and "other" 2 (2.5%). Treatments taken by these 80 individuals included: Activated vitamin D analogues 79 (98.8%); Oral calcium salts 54 (67.5%); "Plain" vitamin D supplements 12 (15%); Thiazide diuretics 5 (6.3%); Oral magnesium supplements 2 (2.5%); rhPTH<sub>1-34</sub> 1 (1.3%) and no individuals in this group were taking phosphate binders or rhPTH<sub>1-84</sub> (Table 1).

In terms of compliance with the audit standards, these were, for the treatment standards: 63.5% for standard 1 (Recommend treatment of all patients with chronic hypoparathyroidism with an albumin adjusted serum calcium level <2.0 mmol/L); 62.5% for standard 2 (Recommend the use of activated vitamin D analogues plus calcium supplements in divided doses as the primary therapy). Patients who had both a vitamin D analogue and a calcium supplement prescribed met the standard; 98.8% for standard 3 (Recommend against the routine use of replacement therapy with PTH or PTH analogues.) and 60.0% for standard 4 (Recommend

vitamin D supplementations in a daily dose of 400–800 IU to patients treated with activated vitamin D analogues) (Figure 1A). However, it should be noted that the compliance with standard 1 was calculated from a partially incomplete data set. Although 40 out of 80 returns demonstrated compliance against this standard (50%), 23 (28.8%) returns demonstrated non compliance. against this standard and a further 17 returns contained incomplete data (21.3%), incomplete data sets arose as a result of biochemical results from the time of diagnosis not being available on the replies. The headline compliance figure of 63.5% was, therefore, calculated as a percentage of the 63 returns containing complete data for this standard.

For compliance with the monitoring standards, these were 77.5% for standard 5 (Recommend routine biochemical monitoring of albumin adjusted serum calcium [e.g., every 3–6 months]); 67.5% for standard 6 (Recommend routine biochemical monitoring of serum phosphate [e.g., every 3–6 months]); 16.3% for standard 7 (Recommend routine biochemical monitoring of serum magnesium [e.g., every 3–6 months]); 63.8% for standard 8 (Recommend routine biochemical monitoring of serum creatinine [e.g., every 3–6 months]); 63.8% for standard 9 (Recommend routine biochemical monitoring eGFR [e.g., every 3–6 months]); 80% for standard 10 (Recommend routine assessment of symptoms of hypocalcaemia and hypercalcaemia at regular time intervals [e.g., every 3–6 months]); 23.8% for standard 11 (Suggest considering monitoring of 24 h urinary calcium excretion at regular intervals [1–2 yearly]); 20% for standard 12 (Recommend renal imaging if a patient has symptoms of renal stone disease or if serum creatinine levels start to rise); and 91.3% for standard 13 (Advise against routine monitoring of BMD by DXA scans) (Figure 1B).

Finally, we found that 13 out of 80 individuals (16.3%) with chronic hypoparathyroidism had experienced at least 1 admission to hospital in the 12 months before the return date, 2 of which were admitted with hypocalcaemia, 3 with cardiac and renal diagnoses and the remainder were unrelated to hypoparathyroidism or were unclear. None (0%) of these individuals had a quality of life survey administered in the preceding 12 months. We did not have any data on how frequently serum vitamin D levels were checked.

Thus, among the 80 returns from 22 endocrine centres across the United Kingdom, overall data completeness was generally very high with only 1 of the 15 standards being open to incomplete assessment due to data completeness and rates of compliance with the 15 audit standards based on consensus recommendations in the European Society for Endocrinology chronic hypoparathyroidism management guidelines<sup>8</sup> ranging from 0% (standard 15, assessment of Quality of life) to 98.8% (standard 3, Recommend against the routine use of replacement therapy with PTH or PTH analogues).

### 4 | DISCUSSION

The Parathyroid UK member survey from 2017<sup>7</sup> showed that only 11% of patients with this condition are regularly receiving care from an endocrinologist specialising in this condition and the PARADOX

**TABLE 1** Detailed breakdown of treatments used

Class of medication	Name of preparation	Number of patients taking medication	Percentage of patients taking medication	Dosage
Oral calcium salt	Calcichew	22	27.5	1–5 Tab/day
	Adcal D3	18	22.5	1–6 Tab/day
	Calcium carbonate	7	8.8	ND
	Sandocal	6	7.5	1–2 Tab/day
	Calfovit	1	1.3	ND
Active vitamin D analogue	Alfacalcidol	69	86.3	0.5–4 mcg/day
	Calcitriol	10	12.5	0.5 mcg/day
“Plain” vitamin D supplements	Ergocalciferol	1	1.3	300,000 IU/3 mths
	Cholecalciferol	11	13.8	2000 IU/day
Thiazide Diuretics	Bendroflumethiazide	3	3.8	2.5 mg/day
	Indapamide	2	2.5	ND
Oral magnesium supplements	ND	2	2.5	ND
rhPTH <sub>1–34</sub>	Teriparatide	1	1.3	20 mcg/day
rhPTH <sub>1–84</sub>	Natpar	0	0	N/A
Phosphate binders	N/A	0	0	N/A
Others	N/A	0	0	N/A

Abbreviations: ND, no data available, N/A, not applicable.

study<sup>11</sup> showed that of 374 individuals with hypoparathyroidism, 72% had experienced more than 10 hypoparathyroidism symptoms in the preceding 12 months and 79% had required an emergency department attendance or hospital admission in the preceding 12 months. It is known that there is an increased risk of renal complications of treatment (Nephrocalcinosis, nephrolithiasis and impaired renal function) in those treated for chronic hypoparathyroidism in comparison to a control population (hazard ratio: 4.31, 95% confidence interval: 2.84–6.52).<sup>12</sup> It is, therefore, clear that there is a clinical need for improvements in routine care of those with chronic hypoparathyroidism and the publication of the ESE and other guidelines<sup>8–10</sup> on the management of chronic hypoparathyroidism is an important step towards improving care. However, if improvements in care and outcome are to be realised it is necessary that there are adequate levels of compliance with the recommendations in these guidelines. We therefore sought to audit compliance with the ESE guidelines<sup>8</sup> main recommendations across UK secondary care endocrine practice.

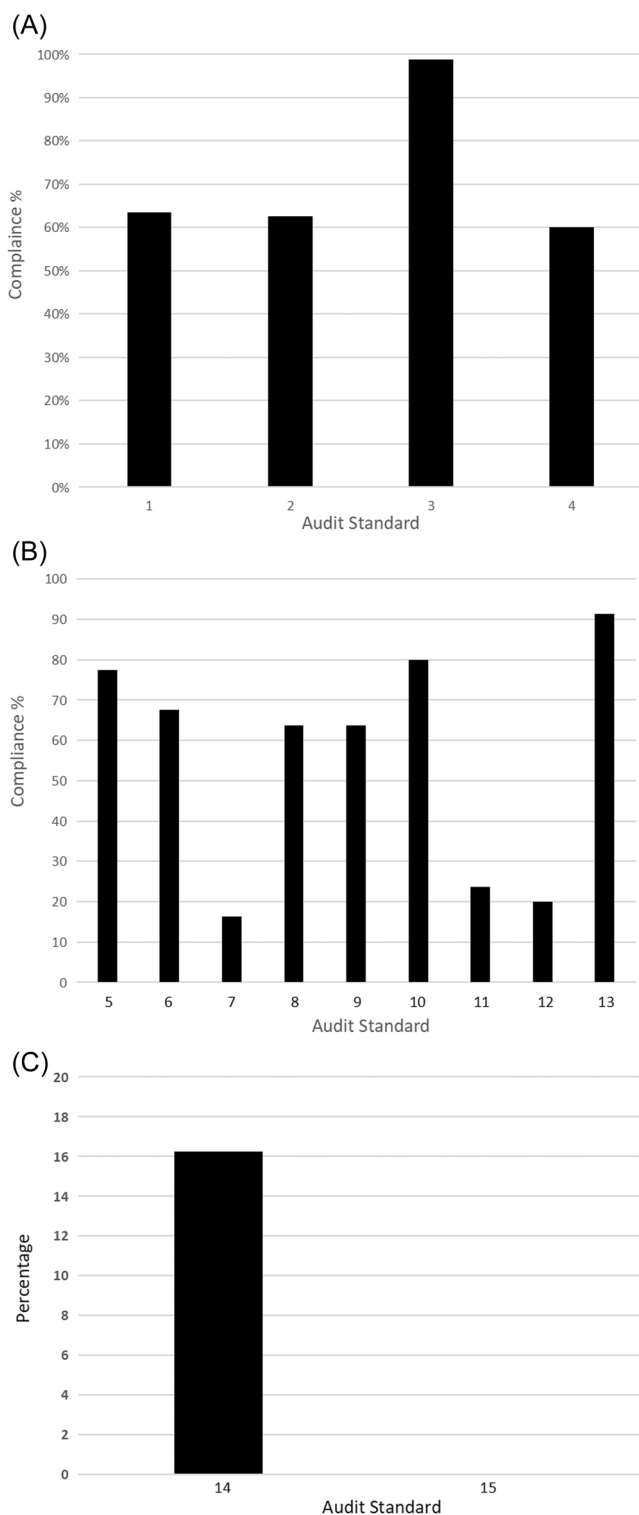
Our results show that among 80 cases of chronic hypoparathyroidism under follow up from 22 different UK endocrine departments, compliance with the audit standards varied between 98.8% and 60% for the treatment standards and between 91.3% and 20% for the monitoring standards. In addition and importantly, 16.3% of subjects had had at least one hospital admission in the preceding 12 months.

We have searched the literature for other similar work where compliance at a national level with hypoparathyroidism guidelines has been reported but can not find any and think that this may be the first systematic national level hypoparathyroidism management audit that has been conducted and reported. Generally speaking there is much scope for improvement in compliance with the guidance in the ESE guidelines<sup>8</sup> used as the basis for the audit standards reported herein and by extension with all of the major international hypoparathyroidism management guidelines.<sup>8–10</sup> It should be noted that in both the Bollerslev<sup>8</sup> and Khan<sup>10</sup> guidelines the quality of evidence for each recommendation was graded by formal methodology and in nearly all cases was graded by the authors as either “low” or “very low”. It will still be important to initiate a quality improvement drive in this field of endocrine practice and then complete the audit cycle with a further national audit of hypoparathyroidism management after a suitable period. One of the quality improvement initiatives that the Society for Endocrinology has recently introduced in this area is the inauguration of the “Endocrine Specialist Network” for bone and calcium disorders.<sup>13</sup> By making regional hubs of expertise available to endocrinologists in each region of the United Kingdom, being available to discuss clinical challenges, raising awareness and running MDT meetings and educational events it is anticipated that over time awareness of and standards

in hypoparathyroidism management will progressively improve. Other quality improvement initiatives will undoubtedly also be necessary. Particular areas for improvement as revealed by the results of our audit will include improvements in routine monitoring and in particular the monitoring of 24 h urinary calcium excretion and ultrasound screening for stone formation

are areas of particularly low attainment at present (Figure 1B) and are particularly worrying as there may be a link between suboptimal management of these factors and potential subsequent development of impaired renal function. Paradoxically, one of the highest areas of attainment in our audit was against audit standard 3 (Recommend against the routine use of replacement therapy with PTH or PTH analogues). It should be born in mind that the ESE guidelines are now over 6 years old<sup>8</sup> and since their publication rhPTH<sub>1-84</sub> ("Natpar" in European markets) has received licensing authorisation from several regulatory bodies.

In terms of strengths and weaknesses of this audit, we think this might be the first time that a national level audit of clinical practice in this field using a major set of international guidelines as the audit standards has been conducted. Data on 80 individual patients in real world care settings gives a robust starting point from which subsequent quality improvement initiatives can be driven. However, the 19% response rate is clearly suboptimal and such a potentially incomplete data set has clear potential to skew the data. For example, the pool of respondents may have been particularly enriched for Society for Endocrinology Bone and Calcium network members or for Parathyroid UK clinical members which could affect the clinical practice and data reflected herein. Causes for the low response rate could include a potentially incomplete set of email addresses used in the original invitations to participate in the audit and also the ongoing COVID-19 pandemic will have meant that many colleagues' clinical practice will have been affected by increased acute medical duties and outpatient clinical capacity reductions.



**FIGURE 1** Audit data organised by audit standard. (A) Treatment standards. (1) Recommend treatment of all patients with chronic Hypoparathyroidism with an albumin adjusted serum calcium level  $<2.0$  mmol/L. (2) Recommend the use of activated vitamin D analogues plus calcium supplements in divided doses as the primary therapy. (3) Recommend against the routine use of replacement therapy with PTH or PTH analogues. (4) Recommend vitamin D supplementations in a daily dose of 400–800 IU to patients treated with activated vitamin D analogues. (B) Monitoring standards. (5) Recommend routine biochemical monitoring of adjusted calcium (e.g., every 3–6 months). (6) Recommend routine biochemical monitoring of phosphate (e.g., every 3–6 months). (7) Recommend routine biochemical monitoring of magnesium (e.g., every 3–6 months). (8) Recommend routine biochemical monitoring of creatinine (e.g., every 3–6 months). (9) Recommend routine biochemical monitoring eGFR (e.g., every 3–6 months). (10) Recommend routine assessment of symptoms of hypocalcaemia and hypercalcaemia at regular time intervals (e.g., every 3–6 months). (11) Suggest considering monitoring of 24-h urinary calcium excretion at regular intervals (1–2 yearly). (12) Recommend renal imaging if a patient has symptoms of renal stone disease or if serum creatinine levels start to rise. (13) Advise against routine monitoring of bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) scans. (C) Additional standards. (14) Percentage of patients who had required inpatient care in the preceding 12 months, (15) Percentage of patients who had undertaken a QoL questionnaire

Another potentially contentious point is that the Bolland guideline mandates the use of oral calcium salts but a growing body of evidence conflicts with this view suggesting that oral calcium salts are not necessarily routine and are only recommended for patients with a dietary calcium deficiency.<sup>14</sup> Finally, the methodology necessarily includes an element of "self assessment" and this too may have the potential to skew the data.

## ACKNOWLEDGEMENTS

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## DATA AVAILABILITY STATEMENT

Data available on request from the authors The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## REFERENCES

1. Powers J, Joy K, Ruscio A, Lagast H. Prevalence and incidence of hypoparathyroidism in the United States using a large claims database. *J Bone Miner Res.* 2013;28(12):2570-2576.
2. Vadiveloo T, Donnan PT, Leese GP. A population-based study of the epidemiology of chronic hypoparathyroidism. *J Bone Miner Res.* 2018;33(3):478-485.
3. Youngwirth L, Benavidez J, Sippel R, Chen H. Parathyroid hormone deficiency after total thyroidectomy: incidence and time. *J Surg Res.* 2010;163(1):69-71.
4. Tecilazich F, Formenti AM, Frara S, Giubbini R, Giustina A. Treatment of hypoparathyroidism. *Best Pract Res Clin Endocrinol Metab.* 2018;32(6):955-964.
5. Bawden D, Fraser W, Turner J, 2021. *The dawn of parathyroid hormone replacement therapy | Society for Endocrinology.* [online] Endocrinology.org.
6. Chadwick D, Kinsman R, Walton P. *Fifth national audit report of the British association of endocrine and thyroid surgeons.* Dendrite Clinical Systems Ltd; 2017:28-106.
7. Parathyroid UK 2017 Living with Hypoparathyroidism.
8. Bolland J, Rejnmark L, Marcolli C, et al. European society of endocrinology clinical guideline: treatment of chronic hypoparathyroidism in adults. *Eur J Endocrinol.* 2015;173(2):G1-G20.
9. Brandi ML, Bilezikian JP, Shoback D, et al. Management of hypoparathyroidism: summary statement and guidelines. *J Clin Endocrinol Metab.* 2016;101(6):2273-2283.
10. Khan AA, Koch CA, Van Uum S, et al. Standards of care for hypoparathyroidism in adults: a Canadian and International Consensus. *Eur J Endocrinol.* 2019;180(3):P1-P22.
11. Hadker N, Egan J, Sanders J, Lagast H, Clarke BL. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. *Endocrine Practice.* 2014;20(7):671-679.
12. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. *J Bone Miner Res.* 2013;28(11):2277-2285.
13. Streamlining NHS. Services with specialised endocrinology networks. *Endocrinologist.* 2021; (issue 139): Spring.
14. Al-Sharefi A, Glenister E, Morris M, Quinton R. Is calcium supplementation always needed in patients with hypoparathyroidism? *Clin Endocrinol.* 2019;90(6):775-780.

## SUPPORTING INFORMATION

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

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