

CLINICAL QUESTION

Elevated PTH with normal serum calcium level: a structured approach

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Summary

Normocalcaemic hyperparathyroidism is a common biochemical finding, usually identified during an assessment of bone or renal health. Hypercalcaemia must be considered by calculation of adjusted calcium, and a careful history taken to assess dietary calcium intake and for the possibility of a malabsorption syndrome. 25-hydroxyvitamin D (25OHD) should be measured and replaced if indicated. The management plan for the patient is influenced by the context in which calcium and PTH were measured. In this brief review we describe the assessment of a patient with normocalcaemic hyperparathyroidism.

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Primary hyperparathyroidism (PHPT) is defined as hypercalcaemia in the presence of high or inappropriately normal parathyroid hormone^{1,2}; there is increasing recognition that a number of patients have a variant with normocalcaemia that could be considered to be a subclinical phase of PHPT.^{1,3,4} The challenge for the managing clinician is to identify and confirm the biochemical abnormality, exclude other causes of hyperparathyroidism, which are more common and include vitamin D deficiency and hyperparathyroidism secondary to chronic kidney disease (Table 1), and assess the clinical context to make an appropriate management plan for the patient.

What is the first step in assessment of the patient with normal calcium and high parathyroid hormone?

In order to confirm that the patient is normocalcaemic, the adjusted serum calcium should be calculated using the formula⁵

$$\text{Adjusted calcium (mmol/l)} = \text{serum calcium} + [(40 - \text{plasma albumin in g}) \times 0.02]$$

In patients with low albumin concentration, calculation of adjusted calcium may reveal hypercalcaemia. This is the method for assessment of calcium concentration recommended by the members of the Fourth International Workshop on Asymptomatic Hyperparathyroidism.¹ Alternatively, adjusted calcium reports may be generated by the reporting laboratory based on the above equation or by a derived regression equation based on the local patient population in question and the performance characteristics of the assay; clinical users should be aware of the method used in their local laboratory (guidance provided at www.weqas.com/download/2011-scientific-session-adjusted-calcium-how-to-do-it/ last accessed 20/1/2016).

Ionized calcium (iCa) measurements are not currently recommended¹; however, there are case reports where iCa revealed hypercalcaemia in patients with parathyroid adenomas.⁶ Blood gas point-of-care (POC) analysers report a measured iCa and a calculated iCa (adjusted to a pH of 7.4); this does not reflect the iCa of a patient with acidosis, in whom iCa is a greater proportion of total calcium. POC-measured iCa can be useful in an emergency setting; however, agreement between POC and laboratory results is less for calcium than for other electrolytes; and POC performance is dependent on staff training and quality control standards.⁷ We use an ion electrode iCa measurement, which is reported as measured (not corrected with pH of 7.4); this was a decision taken because of the high prevalence of acid-base disturbance in our local cohort.⁸ Adjusted calcium is unreliable in the setting of very low albumin and in this circumstance it would be appropriate to measure ionized calcium.⁹

What is the role of 25-hydroxyvitamin D (25OHD) measurement in assessment of the patient with normocalcaemic hyperparathyroidism?

Normocalcaemic hyperparathyroidism may be secondary to vitamin D deficiency. It is unlikely that elevated PTH would be secondary to vitamin D deficiency alone if 25OHD is greater than 50 nmol/l, at which level the bone health requirements of 97.5%

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Table 1. Differential diagnosis of normocalcaemic hyperparathyroidism

Primary hyperparathyroidism Parathyroid adenoma/hyperplasia	Acute illness Pancreatitis; septicaemia; toxic shock; rhabdomyolysis; prolonged intensive care admission; possibly adrenal crisis
Vitamin D deficiency Reduced sunlight exposure; reduced dietary intake; liver disease	Malabsorption/dietary Restrictive/exclusion diets; coeliac disease; chronic pancreatitis
Chronic kidney disease Reduced 1,25 (OH) ₂ vitamin D; increased stimulation of PTH by phosphate; increased circulating inactive PTH/PTH fragments	Drug therapy Anticonvulsants; bisphosphonates; denosumab; steroids; lithium; proton pump inhibitors; phosphate supplementation <i>Note:</i> normocalcaemia with mildly elevated PTH is the treatment target in patients receiving cinacalcet therapy in end-stage renal disease

of the population are met.¹⁰ The most appropriate assessment of vitamin D status is by measurement of total 25OHD. An inverse relationship between 25OHD and PTH has been reported in population studies and subgroups such as postmenopausal women.^{11,12} There is no fixed 25OHD measurement at which PTH begins to rise; multiple other factors, such as dietary calcium intake and magnesium, influence this interaction.¹³

Interpretation of the impact of vitamin D on bone health and PTH, and on extra-skeletal effects of vitamin D has not been standardized across all studies and thus the Endocrine Society and Institute of Medicine have made different recommendations regarding vitamin D replacement.^{10,14} Part of the discrepancy between the recommendations may be due to the mathematical assessment of measured 25OHD response to oral dosing with vitamin D - an analysis of the primary data showed that this response was about 5.3 nmol/l per 100 IU per day which was twice the response estimated by the Endocrine Society in making a dose recommendation. The IOM also took individual sunlight exposure into account in its estimation of bone health risk.¹⁵ The National Osteoporosis Society UK largely follows IOM recommendations,¹⁶ and recommends loading doses to a total of 300 000 IU over 6–10 weeks in symptomatic cases. In less urgent cases, our experience is that replacement can be achieved with doses of 800 IU per day, up to 2000 IU, without loading.¹⁷ In some patients with normocalcaemic hyperparathyroidism replacement of vitamin D leads to a rise in calcium and thus 'unmasks' primary hyperparathyroidism; this is reflected in the National Osteoporosis Society UK recommendation to re-check serum calcium 1 month after vitamin D loading or commencement of supplementation.^{2,16,18} In a 2015 study that included 23 patients with PHPT, vitamin D deficiency and normal calcium, 6 months' treatment with 1600–3200 IU per day did not provoke hypercalcaemia.¹⁹

What is the clinical context for the patient with normocalcaemic hyperparathyroidism?

There is no indication to test PTH in a patient with normocalcaemia unless this is done as part of a bone health or renal review. Therefore, the clinical context in which the measurement of calcium and PTH was made determines the management plan.

In patients with chronic kidney disease (CKD) guidance for management of hyperparathyroidism has been provided by the Kidney Disease: Improving Global Outcomes (KDIGO) group

(Table 2).²⁰ KDIGO guidelines recommend evaluation of vitamin D status and hyperphosphataemia for those patients with CKD stage 3–5, for whom the optimal range of PTH is not known; and monitoring of PTH to identify those with increasing PTH who may benefit from calcitriol therapy.²⁰ For those with CKD stage 5 who are on dialysis, there is a wide range of 'target' PTH (2–9 times the upper limit of normal for the PTH assay) because of lack of evidence for bone or cardiovascular benefit from targeting tighter PTH ranges in the endstage renal disease population, and because of the cross-reaction of PTH fragments in endstage renal disease with some assays.^{20,21} Bone biopsy is recommended in cases of uncertain aetiology or if an anti-resorptive agent is being considered; in practice we find it useful to discuss these cases with the managing nephrologist and rarely perform biopsy.

History and examination should identify whether the patient is at risk of poor calcium intake or malabsorption of dietary calcium, or taking a medication such as phenytoin which would interfere with vitamin D metabolism (Table 1).^{13,22}

In the absence of chronic kidney disease, malabsorption or deficiency of active vitamin D, normocalcaemic hyperparathyroidism may represent a subclinical form of PHPT,²³ described as a *forme fruste* by Silverberg and Bilezikian³; it is reported to be common in population studies, although prevalence rates vary according to the diagnostic criteria applied.²⁴ A recent analysis of data from the Dallas Heart Study revealed a prevalence of normocalcaemic PHPT of 3.1% in a community population²⁵; in the longitudinal WHO MONICA study prevalence increased over 13 years of follow-up from 2.0% to 11.0% in a study population aged 38–79 years.²⁶ In a clinical context where a patient is having a bone health assessment after fracture this is a relevant diagnosis, because a fragility fracture is a clear indication for surgical management of PHPT.²⁷

In the context of a patient being identified while having a bone health screen in the absence of fracture the management plan is less clear. The natural history of normocalcaemic hyperparathyroidism is that around 20% of these patients develop hypercalcaemia at follow-up of 3–8 years.^{28,29} We have observed in clinical practice that some of these patients may become hypercalcaemic during times of immobility or after exposure to a thiazide diuretic, and that this can revert to normocalcaemia after resumption of normal activity or withdrawal of the drug.

Monitoring of calcium alone in subjects with normocalcaemic hyperparathyroidism is insufficient to identify patients at risk of bone or kidney complications of PHPT; in one study of 37

Table 2. Summary of KDIGO guidelines for CKD-MBD (adults)²⁰

CKD Stage 3	<ul style="list-style-type: none"> • Start monitoring Ca, P, PTH • Ca & P every 6–12 months; PTH based on progression • Keep Ca & P in normal range (Phosphate binders) • 25OHD check; treat as per general population
CKD Stage 4	<ul style="list-style-type: none"> • PTH in normal range; treat osteoporosis as per general population • Ca & P check every 3–6 months; PTH every 6–12 months • Keep Ca & P in normal range (Phosphate binders) • Alk Phos every 12 months, more if PTH increased • 25OHD check; treat as per general population
CKD Stage 5, including dialysis	<ul style="list-style-type: none"> • Consider bone biopsy before use of anti-resorptive agent • Ca & P check every 1–3 months; PTH every 3–6 months • Keep Ca & P in normal range (Phosphate binders) • If on dialysis keep Ca normal and lower elevated P towards normal • Alk Phos every 12 months, more if PTH increased • Keep PTH between 2–9 times upper limit normal, using calcitriol, vitamin D analogues, calcimimetic alone or in combination • 25OHD check; treat as per general population • Consider bone biopsy before use of anti-resorptive agent
General Comments	<ul style="list-style-type: none"> • Use trends over time rather than single values • Close liaison with laboratory services and familiarity with assays aids interpretation of results • Consider bone biopsy in cases of uncertain aetiology • BMD measurement not as useful for fracture risk evaluation as in general population • Restrict Ca-based Phosphate binders if hypercalcaemia/arterial calcification/adynamic bone • Optimal PTH if not on dialysis, is not known • Any patient with severe hyperparathyroidism that does not respond to medical therapy should be considered for parathyroidectomy

Ca, calcium; P, phosphate; MBD, mineral bone disease.

patients, seven became hypercalcaemic but a further six experienced BMD loss of >10% and there was a case of renal calculus and one of fracture.²⁹ In a recent study which compared 23 patients with normocalcaemic PHPT to 284 who had PHPT with hypercalcaemia there were no differences in prevalence of low BMD or nephrolithiasis between the groups, albeit in a retrospective study with a small number of normocalcaemic cases.³⁰ Another study which compared normocalcaemic to hypercalcaemic PHPT patients suggested that the prevalence of nephrolithiasis was equal in both cohorts but that hypercalcaemia was associated with more fractures, although this difference did not reach significance.³¹ Apart from bone and renal health, there is some evidence that normocalcaemic PHPT is associated with an increased risk of hypertension.^{26,32} Therefore, normocalcaemic PHPT cannot be considered to have a completely benign clinical course and it is appropriate to use the guidelines for management of asymptomatic hyperparathyroidism when following up these cases.¹ It should be remembered that in asymptomatic hyperparathyroidism active screening for vertebral fractures and nephrolithiasis reveals a prevalence of about 35% for these complications.³³ Parathyroidectomy has been shown to improve BMD at 1 year after surgery in normocalcaemic PHPT.³⁴

Although we have here described patients with end-organ effects that would be likely to benefit from parathyroidectomy, there are a number of patients who have normocalcaemic hyperparathyroidism, that is identified on 'health screening' or a generalized battery of biochemical work-up, outside the setting

of bone or renal disease. It is much harder to make clinical decisions for such patients for whom the benefit of intervention is likely to be less than patients with fractures or nephrolithiasis. For such patients we advocate an individual discussion with the patient, taking into account any co-morbidities, the patient's own concerns and wishes and the probable follow-up plan should a watch-and-wait policy be pursued. In monitoring patients who do not undergo parathyroidectomy we measure calcium, phosphate, 25OHD and PTH yearly and consider renal US and DXA every 3–5 years.

Conclusion

Normocalcaemic hyperparathyroidism is common and may have implications for bone and renal health. Normocalcaemia should be confirmed by calculation of adjusted calcium and measurement of ionized calcium in case of marked hypoalbuminaemia. KDIGO has provided guidelines for management of patients with normocalcaemic hyperparathyroidism in the setting of chronic kidney disease. For those patients with normocalcaemic hyperparathyroidism identified as part of a bone health assessment, the management plan should be individualised according to the patient's history of fracture, nephrolithiasis and renal function and consideration should be given to measurement of bone mineral density and renal tract imaging. The appropriateness of parathyroidectomy for normocalcaemic hyperparathyroidism needs to be considered in light of these patient-specific variables.

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Nothing to declare

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