Endocrine Intelligence

Endocrine Intelligence · 03/10/2026, 6:07:09 UTC

Clinical question

50 year old with High calcium, mildly high PTH. Urine calcium creatinine clearance ratio is 0.014. Vitamin D over 50

Answer

Interpretation of Biochemical Profile

In a 50-year-old with hypercalcaemia, a mildly elevated intact PTH, and a 25-hydroxyvitamin D level above 50 ng/mL, the working diagnosis is **primary hyperparathyroidism (PHPT)** until proven otherwise. The vitamin D repletion is important: it excludes secondary hyperparathyroidism from vitamin D deficiency as a confounder, and it removes one of the common reasons urinary calcium excretion might be spuriously low (which could otherwise mimic FHH). The mildly elevated PTH in the setting of hypercalcaemia is the hallmark biochemical signature of PHPT; even a PTH that is "technically normal" is inappropriately elevated when calcium is high, and the Fifth International Workshop confirms that PHPT is the diagnosis in hypercalcaemic patients with a PTH that is not suppressed.

The Calcium-to-Creatinine Clearance Ratio of 0.014

This is the critical discriminating value in the differential between PHPT and familial hypocalciuric hypercalcaemia (FHH), and 0.014 falls squarely in the **overlap zone (0.01–0.02)**:

- A ratio **< 0.01** favours FHH (present in 70–80 % of FHH subjects), but up to 20 % of PHPT patients can also fall below 0.01.
- A ratio **> 0.02** is more typical of PHPT, but up to 10 % of FHH patients can exceed 0.02.
- Approximately **40 % of patients with either condition** have values between 0.01 and 0.02.

Therefore, a ratio of 0.014 **does not exclude FHH**, but it also does not strongly favour it. In a 50-year-old, FHH is less likely on epidemiological grounds: the Workshop notes that FHH should be particularly suspected in patients under 30, those with lifelong hypercalcaemia, or those with a family history of hypercalcaemia. If this patient has no such history, the pre-test probability of FHH is low, and the ratio of 0.014 is more consistent with PHPT.

Additional Exclusions Before Confirming PHPT

Before labelling this as PHPT, the following should be verified:

- **Medications**: Thiazide diuretics and lithium can raise both calcium and PTH. If either is in use, the calcium should be rechecked several months after withdrawal; hypercalcaemia that persists after stopping the drug points toward PHPT.
- **Biotin interference**: High-dose biotin supplements can falsely lower PTH on some immunoassays. Discontinue biotin for at least 48 hours before repeating the PTH.
- **Renal function**: Ensure the patient does not have end-stage kidney disease (which would suggest tertiary hyperparathyroidism) or moderate CKD that could alter the interpretation.
- **Repeat testing**: Confirm the hypercalcaemia and PTH elevation on at least two occasions over 3–6 months, using a second- or third-generation intact PTH assay, after excluding secondary causes.

Role of Genetic Testing for FHH

The 2026 case series from an endocrine practice (25 patients with likely FHH) reinforces that **traditional biochemical methods—24-hour urinary calcium and the calcium-to-creatinine clearance ratio—are not adequate in isolation to distinguish FHH from PHPT**. In that series, the CCCR was < 0.01 in only 45 % of confirmed FHH cases, and 24-hour urinary calcium was often > 100 mg/24 h. The authors recommend that **molecular testing (CASR, GNA11, AP2S1) should be considered before parathyroid surgery** when hypercalcaemia cannot be clearly demonstrated to be acquired, and in cases of persistent hypercalcaemia after surgery. In this 50-year-old with a ratio in the overlap zone, if there is any family history of hypercalcaemia, unexplained prior parathyroid surgery, or atypical features, targeted genetic testing is reasonable before proceeding to surgery. In the absence of such red flags, the clinical picture favours PHPT and the ratio of 0.014, while not excluding FHH, is more consistent with a primary parathyroid adenoma or hyperplasia.

Recommended Workup if PHPT Is Confirmed

Once the diagnosis is secured, the standard assessment per the Fifth International Workshop and NICE NG132 includes:

- **Biochemistry**: Adjusted total calcium (or ionised calcium), phosphorus, intact PTH, 25-OH-D, creatinine/eGFR, and a **full 24-hour urinary calcium** (the clearance ratio is a screening tool; the 24-hour collection also identifies hypercalciuria, which is a surgical indication and a stone-risk factor).
- **Skeletal**: Three-site DXA (lumbar spine, total hip, distal 1/3 radius); vertebral fracture assessment (VFA) or lateral spine X-rays; trabecular bone score if available.
- **Renal**: eGFR or creatinine clearance; renal ultrasound for nephrolithiasis/nephrocalcinosis; if hypercalciuria is present, a stone-risk profile.
- **Symptom review**: Neurocognitive and quality-of-life assessment, as these are common non-classical manifestations.

Summary

The combination of hypercalcaemia, mildly elevated PTH, and vitamin D repletion in a 50-year-old is most consistent with **primary hyperparathyroidism**. The calcium-to-creatinine clearance ratio of 0.014 sits in the 0.01–0.02 overlap zone and does not by itself confirm or exclude FHH, but in the absence of young age, lifelong hypercalcaemia, or a positive family history, FHH is unlikely. Confirm the diagnosis with repeat biochemistry (excluding biotin, thiazides, lithium, and renal impairment), complete the standard PHPT workup, and consider CASR/GNA11/AP2S1 genetic testing if any clinical feature raises residual suspicion for FHH before surgical referral.

Evidence and citations

[1] Evaluation and Management of Primary Hyperparathyroidism: Fifth International Workshop
International Workshop on Primary Hyperparathyroidism
https://www.endocrinology.org/media/boodt50x/bilezikian-et-al-guidelines.pdf

Supporting passage supplied to the model

> What is the differential diagnosis of hypercalcemia and elevated levels of PTH? 1. 2. 1. Familial hypocalciuric hypercalcemia (FHH) may be suspected in younger individuals with a urinary calcium /creatinine clearance ratio <0. 01 and/or those with a family history of hypercalcemia. 1. 2. 2. Thiazide diuretics and lithium (see text) 1. 2. 3. Ectopic secretion of PTH (very rare) 1. 3. Normocalcemic PHPT: normal adjusted total calcium and normal ionized calcium levels along with elevated intact PTH (utilizing either a second or third generation assay) on at least two occasions over 3–6 months after all alternative causes for secondary hyperparathyroidism have been ruled out. 2. What are the clinical phenotypes of PHPT? 2. 1. Symptomatic PHPT: associated with overt skeletal and renal complications that may include osteitis fibrosa cystica and/or fractures, chronic kidney disease, nephrolithiasis and/or nephrocalcinosis 2. 2. Asymptomatic PHPT: no overt symptoms or signs; typically discovered by biochemical screening. Two forms of asymptomatic PHPT are defined after evaluation: 2. 2. 1. with target organ involvement 2. 2. 2. without target organ involvement 2. 3.

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> Up to 20% of patients with PHPT can have a calcium-creatinine clearance (Ca/Cr Cl) ratio <0. 01 and up to 10% of patients with FHH can have Ca/Cr Cl ratio >0. 02, a range that is more commonly seen in PHPT. About 40% of patients with either disease can have values between 0. 01 and 0. 02. (84–87) Another point to bear in mind is that urinary calcium measurements are not likely to be accurate if patients are on lithium or thiazide diuretics. Vitamin D deficiency or chronic kidney disease can also be associated with reduced urinary calcium excretion. FHH becomes an important point to consider in patients whose n6 BILEZIKIAN ET AL. hypercalcemia is lifelong, if they are under 30 years old, or have a family history of hypercalcemia. (3) As noted above, genetic testing is indicated when FHH is a consideration. Another differential point related to lithium or thiazides is that either medication can be associated with hypercalcemia and PTH level above normal. More often than not, the history of these medications leads to a diagnosis of PHPT. If the medication is withdrawn, and the serum calcium is retested several months later, hypercalcemia is likely still to be present.

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[9] Clinical and molecular characterization of familial hypocalciuric hypercalcemia in an endocrine practice: a case series of 25 patients.
Europe PMC
https://pubmed.ncbi.nlm.nih.gov/42038813/

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> Familial hypocalciuric hypercalcemia (FHH) is a disorder caused by abnormal sensing of calcium by the parathyroids and renal tubules and may mimic primary hyperparathyroidism (PHPT). Patients with FHH should not be subjected to unnecessary and potentially harmful parathyroid surgery. We sought to evaluate the clinical and biochemical presentation of FHH in our endocrine practice. This was a retrospective chart review done after Institutional Review Board approval. We describe 25 cases of likely FHH from our endocrine practice (20 FHH1, 1 FHH2, and 4 FHH3). The 24-h urinary calcium levels were often greater than 100 mg/24 h and sometimes greater than 200 mg/24 h. The calcium to creatinine clearance ratio (CCCR) was consistently <0.01 in 10 of 22 (45%). We also describe several variants of CASR and 1 variant of GNA11 that are probably pathogenic. Some patients, particularly FHH3 patients, have hypercalcemia severe enough to warrant treatment with a calcimimetic medication (cinacalcet). Traditional methods of excluding FHH using 24-h urinary calcium and CCCR are not adequate to distinguish FHH and PHPT. In addition to young age, family history of hypercalcemia and low CCCR, we believe molecular testing should be considered prior to surgery when hypercalcemia cannot be demonstrated to be acquired and in the case of persistent PHPT after surgery by an experienced parathyroid surgeon.

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> Measure adjusted total serum calcium (ionized if NPHPT is a consideration), phosphorus, intact PTH, 25OHD, creatinine Skeletal: 2. Three-site DXA (lumbar spine, hip, distal 1/3 radius); imaging for vertebral fractures (VFA or vertebral X-rays). As an adjunctive test, the TBS can be helpful if available. Renal: 3. eGFR or, preferably, creatinine clearance, full 24-hour urinary calcium. Imaging for nephrolithiasis/nephrocalcinosis. In those with hypercalciuria, a stone risk profile is recommended. In those with stones (an indication for surgery) a stone risk profile is recommended whether or not the patient has hypercalciuria. Evaluation of nonclassical manifestations Neurocognitive and quality of life One of the most frequent but nonclassical manifestations of PHPT relates to neurocognitive or neuropsychiatric function. Although there is no doubt that symptomatic PHPT with severe hypercalcemia can be associated with altered mental status,(140) it is uncertain if more subtle manifestations of neurocognitive function relate specifically to PHPT when the serum calcium is not markedly elevated.

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[14] Primary hyperparathyroidism: diagnosis, assessment and initial management

National Institute for Health and Care Excellence

https://www.nice.org.uk/guidance/ng132/resources/hyperparathyroidism-primary-diagnosis-assessment-and-initial-management-pdf-66141715991749

Supporting passage supplied to the model

> 2 To differentiate primary hyperparathyroidism from familial hypocalciuric hypercalcaemia, measure urine calcium excretion using any one of the following tests: • 24-hour urinary calcium excretion • random renal calcium:creatinine excretion ratio • random calcium:creatinine clearance ratio. © NICE 2024. All rights reserved. Subject to Notice of rights (https://www. nice. org. uk/terms-andconditions#notice-of-rights). Page 8 of 36 Hyperparathyroidism (primary): diagnosis, assessment and initial management (NG132) Assessment after diagnosis 1. 2. 3 For people with a confirmed diagnosis of primary hyperparathyroidism: • assess symptoms and comorbidities • measure eGFR (estimated glomerular filtration rate) or serum creatinine • do a DXA (dual-energy X-ray absorptiometry) scan of the lumbar spine, distal radius and hip • do an ultrasound scan of the renal tract. For a short explanation of why the committee made the recommendations and how they might affect practice, see the rationale and impact section on testing and assessment in secondary care.

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[17] Is routine 24-hour urine calcium measurement useful during the evaluation of primary hyperparathyroidism?

Europe PMC

https://pubmed.ncbi.nlm.nih.gov/34325903/

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> <h4>Background</h4>Primary hyperparathyroidism and familial hypocalciuric hypercalcemia have similar biochemical profiles, and calcium-to-creatinine-clearance ratio helps distinguish the two. Additionally, 24-hour urine calcium >400 mg/day indicates surgery and guidelines recommend obtaining 24-hour urine calcium preoperatively. Our aim was to assess how 24-hour urine calcium altered care in the evaluation of suspected primary hyperparathyroidism.<h4>Methods</h4>Consecutive patients assessed for primary hyperparathyroidism from 2018 to 2020 were reviewed. Primary hyperparathyroidism was diagnosed by 2016 American Association of Endocrine Surgeons Parathyroidectomy Guidelines criteria. 24-hour urine calcium-directed change in care was defined as familial hypocalciuric hypercalcemia diagnosis, surgical deferment for additional testing, or 24-hour urine calcium >400 mg/day as the sole surgical indication.<h4>Results</h4>Of 613 patients, 565 (92%) completed 24-hour urine calcium and 477 (84%) had concurrent biochemical testing to calculate calcium-to-creatinine-clearance ratio. 24-hour urine calcium was <100 mg/day in 9% (49/565) and calcium-to-creatinine-clearance ratio was <0.01 in 17% (82/477). No patient had confirmed familial hypocalciuric hypercalcemia, although 1 had a CASR variant of undetermined significance. When calcium-to-creatinine-clearance ratio was <0.01, familial hypocalciuric hypercalcemia was excluded by 24-hour urine calcium >100 mg/day (56%), prior normal calcium (16%), renal insufficiency (11%), absence of familial hypercalcemia (3%), normal repeat 24-hour urine calcium (10%), or interfering diuretic (1%). 24-hour urine calcium-directed change in care occurred in 25 (4%), including 4 (1%) who had genetic testing. Four-gland hyperplasia was more common with calcium-to-creatinine-clearance ratio <0.01 (17% vs calcium-to-creatinine-clearance ratio ≥ 0.01, 4%, P < .001), but surgical failure rates were equivalent (P = .24).<h4>Conclusion</h4>24-hour urine calcium compliance was high, and results affected management in 4%, including productive identification of hypercalciuria as the sole surgical indication in 2 patients. When calcium-to-creatinine-clearance ratio <0.01, clinical assessment was sufficient to exclude familial hypocalciuric hypercalcemia and only 1% required genetic testing. 24-hour urine calcium should be ordered judiciously

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