Chapter 6 / Capítulo 6

Electrolyte and Internal Environment Imbalances in Emergencies (English Edition)
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Hypercalcemia in Emergency Care

Hipercalcemia en emergencia

Jorge Márquez Molina[1], Mauricio Paz del Río[2], Willy Eustaquio Mollo Marca[3]

[1]Hospital del Norte. Cochabamba, Bolivia.
[2]Hospital Municipal de Cotahuma. La Paz, Bolivia.
[3]Hospital General San Juan de Dios. Oruro, Bolivia.

Objectives:

- Understand the normal physiology of calcium and its hormonal regulation.
- Identify the main causes of hypercalcemia.
- Apply pathophysiological mechanisms to the evaluation and treatment of patients in emergency settings.

INTRODUCTION

Patients with hypercalcemia present a spectrum ranging from asymptomatic to coma, depending on the degree and chronicity of hypercalcemia.

It is possible that total serum calcium levels do not accurately correlate with the physiologically active free form of calcium, this can be estimated by calculating corrected calcium to adjust for the calcium bound to serum albumin, or by directly measuring the ionized calcium level.

Clinical case

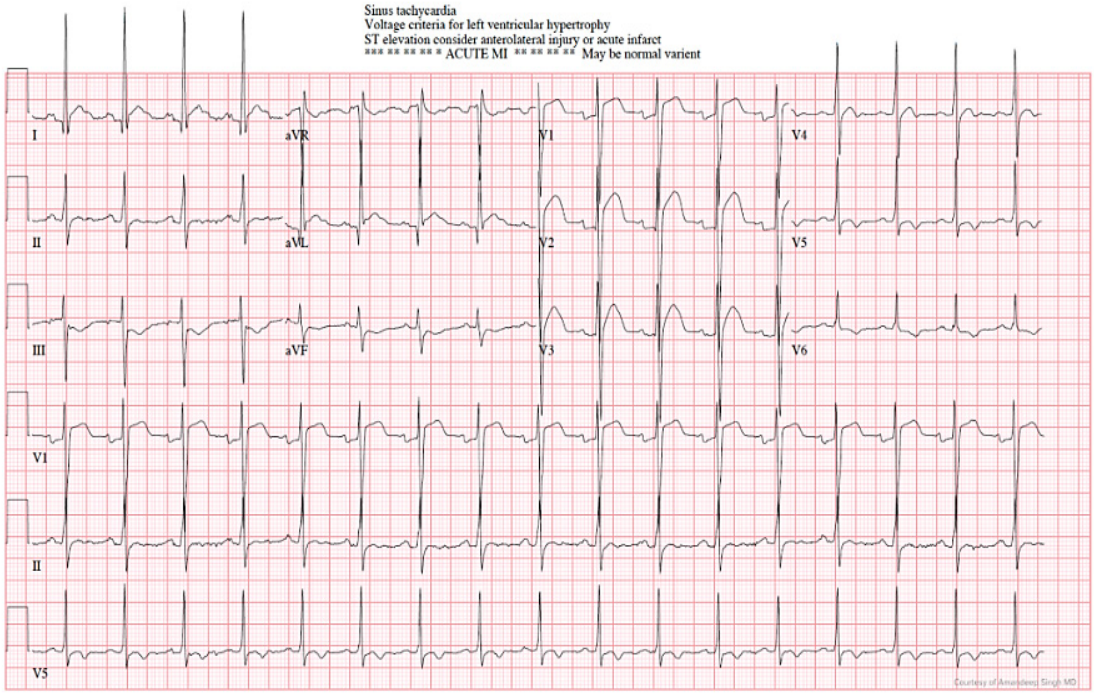

Figure 6.1. Electrocardiogram of the clinical case

For interpretation, the following clinical case is presented: a 64-year-old male patient, with a history of lung carcinoma, presents to the emergency room due to persistent vomiting and progressive alteration of mental status. On physical examination, he shows dry mucous membranes and evidence of dehydration. Diffuse pain is noted on palpation of muscles and bones, accompanied by generalized weakness. The patient is confused and responds incoherently to questions. An electrocardiogram is performed, revealing shortened PR and QT intervals, a finding consistent with significant hypercalcemia.

TIPS: *Most patients with significant hypercalcemia have severe depletion of intravascular volume, and fluid replacement is the cornerstone of treatment.*

In the anamnesis

Ask about the history of known hypercalcemia, parathyroid disease, or malignancy. These are the most common historical risk factors and underlying etiologies of hypercalcemia.

It is essential to inquire about symptoms that guide the diagnosis of hypercalcemia and determine the urgency of studies and treatment. Classically, the clinical manifestations are summarized by the mnemonic rule "stones, bones, groans, thrones, and psychiatric overtones", which reflects the broad multisystem manifestations of excess serum calcium.

- "Stones" refer to the presence of kidney stones due to recurrent nephrolithiasis, sometimes accompanied by renal insufficiency secondary to prolonged hypercalciuria. "Bones" allude to skeletal system involvement, with diffuse bone pain, arthralgias, and loss of bone mineral density, manifestations that may progress to osteoporosis or pathological fractures.
- Abdominal "groans" correspond to gastrointestinal symptoms such as nausea, vomiting, anorexia, and abdominal pain, occasionally associated with acute pancreatitis induced by hypercalcemia. The term "thrones" is linked to polyuria and polydipsia, resulting from acquired nephrogenic diabetes insipidus, a consequence of reduced renal concentrating capacity due to tubular damage. Finally, "psychiatric overtones" include manifestations ranging from lethargy and altered mental status to hallucinations, depression, or coma, reflecting neurological and cerebral involvement secondary to elevated calcium levels.

During the physical examination

A complete neurological and psychiatric evaluation is recommended, since the central nervous system is particularly sensitive to alterations in serum calcium. Even mild hypercalcemia may manifest as an organic cause of neuropsychiatric disorders, including anxiety, irritability, depression, or decreased concentration and memory. As calcium levels rise, neurological involvement becomes more evident, with possible presentation of drowsiness, confusion, disorientation, and, in the most severe cases, profound obtundation or coma.

Diagnostic tests

In every patient with suspected hypercalcemia, basic studies should be requested to confirm the diagnosis, identify the cause, and assess possible systemic complications.

A complete blood count is useful to rule out anemia or associated hematologic processes, such as multiple myeloma. A comprehensive metabolic panel allows measurement of total serum calcium and plasma albumin, in order to calculate corrected calcium and simultaneously evaluate renal function, which is often compromised by dehydration or nephrocalcinosis. Likewise, serum levels of phosphorus and magnesium should also be quantified, since concomitant electrolyte disorders are common and may modify the clinical presentation or complicate interpretation of results.

The electrocardiogram (ECG) is an essential tool in the initial evaluation, as patients with hypercalcemia may develop significant cardiovascular alterations, including shortening of the QT interval, atrioventricular blocks, and, in severe cases, potentially lethal ventricular arrhythmias. These electrocardiographic findings reflect decreased myocardial excitability induced by elevated serum calcium.

Additional tests to consider

Depending on the clinical context and the severity of the condition, complementary studies may be required to confirm the pathophysiological nature of hypercalcemia or to identify its complications.

Measurement of ionized calcium is the most accurate way to assess physiologically active calcium, as it is not affected by variations in albumin concentration or by the patient's acid–base status. Its determination is particularly useful in intensive care units or in patients with marked hypoalbuminemia.

In cases presenting with severe abdominal pain or persistent vomiting, serum lipase measurement is indispensable to rule out acute pancreatitis, a potentially serious complication induced by hypercalcemia.

Quantification of parathyroid hormone (PTH) is an essential test in etiological evaluation, as it allows differentiation between hypercalcemia of parathyroid origin (elevated PTH) and non-parathyroid hypercalcemia (suppressed PTH), as occurs in neoplasms, hypervitaminosis D, or granulomatous processes.

When there is suspicion of primary or metastatic pulmonary neoplasm, a chest radiograph is recommended to identify masses, nodules, or costal osteolytic lesions. Finally, in patients with significant alteration of mental status, a cranial computed tomography scan should be considered to exclude other neurological causes or concomitant intracranial lesions that may contribute to neurological deterioration.

Treatment

Initial stabilization (always)

- ABC first: ensure a protected airway and effective ventilation.
- Monitoring: vital signs, hourly urine output, telemetry/ECG.
- Rapid corrections: treat hypovolemia, nausea/vomiting, and correct K^+/Mg^{2+} and phosphorus if altered.

Confirmation and stratification

Confirm with corrected or ionized calcium. Classify severity according to corrected calcium and symptoms:

- Mild: 10,5–12 mg/dL (2,6–3,0 mmol/L)
- Moderate: 12–14 mg/dL (3,0–3,5 mmol/L)
- Severe (crisis): ≥14 mg/dL (≥3,5 mmol/L) or neurological/cardiovascular involvement

ECG note: Shortened QT interval, risk of atrioventricular blocks and ventricular arrhythmias → monitoring.

Fluid resuscitation (cornerstone)

- Initial crystalloid bolus (preferably 0,9 % NaCl) until blood pressure/perfusion is normalized (use dynamic parameters when possible).
- Maintenance infusion: 0,9 % NaCl at 200–300 mL/h (adjust to achieve urine output ≈2 L/day).

- Caution: in heart failure or chronic kidney disease (CKD) → titrate more slowly, consider pulmonary ultrasound/BIA if available.
- Loop diuretic (furosemide): only if overload occurs after resuscitation.

Recommendation: the routine use of furosemida in the treatment of hypercalcemia is no longer recommended and should be reserved for cases of iatrogenic volume overload and for patients with heart failure or renal insufficiency.

Rapid reduction (bridge): Calcitonin

Calcitonin 4 IU/kg SC/IM every 12 hours.

- Onset at 4–6 hours; tachyphylaxis at 48–72 hours → use as a bridge therapy.
- Contraindication: salmon allergy (formulation is derived from salmon).

Sustained control (antiresorptives)

After adequate hydration, choose one:

- Zoledronic acid: 4 mg IV over ≥15 minutes.
  - Consider acetaminophen post-infusion (acute "flu-like" reaction).
  - Avoid if serum creatinine >4,5 mg/dL or severely reduced GFR.
- Pamidronate: 60–90 mg IV over ≥4–6 hours (better renal safety than over 2 hours).
  - Avoid if serum creatinine >4,5 mg/dL.
- Ibandronate: 2–6 mg IV over 1–2 hours.
  - Avoid if creatinine clearance <30 mL/min.
- If advanced CKD or refractory cases:
  - Denosumab 120 mg SC (off-label in some guidelines for malignant hypercalcemia/CKD). Useful when bisphosphonates are not appropriate.

Tip: Hydrate before antiresorptives; their full effect takes 24–48 hours.

Targeted therapies according to etiology

Hypercalcemia due to vitamin D / lymphoma / sarcoidosis:

- Corticosteroids (after coordination with treating physician/oncology):
  - Hydrocortisone 200 mg IV/day for 3 days, or
  - Prednisone 20–40 mg PO/day.
- Hyperparathyroidism (elevated PTH):
  - Cinacalcet (calcimimetic): 30–60 mg PO every 12–24 hours (chronic management; coordinate with endocrinology).
- Causative drugs: discontinue thiazides, high doses of vitamin A/D, lithium, etc.

Dialysis (rescue therapy)

Indicated in:

- Severe hypercalcemia with neurological or cardiac symptoms and failure of medical measures.
- Advanced CKD with fluid overload or contraindication to antiresorptive agents.
- Objective: rapid removal of calcium and correction of blood volume.

***TIPS**: a nephrology consultation should be considered for hemodialysis in severe cases of hypercalcemia that are refractory to medical treatment or associated with cardiac dysfunction (e.g., arrhythmia, heart block) or severe neurological symptoms (e.g., coma).*

Special populations

Pregnancy

- IV fluids (0,9 % NaCl) as the foundation.
- Avoid bisphosphonates (potential teratogenicity).
- Coordinate with obstetrics; consider calcitonin as bridge therapy.

Pediatrics

- 0,9 % NaCl bolus: 20 mL/kg.
- Infusion: sodium chloride at twice maintenance (adjust according to clinical status).
- Calcitonin 4 IU/kg SC/IM every 12 hours.
- Pamidronate 1–2 mg/kg IV (max. 90 mg) over 4–6 hours.

Renal / cardiac insufficiency

- Hydrate cautiously; monitor for congestion (weight, lung ultrasound, BNP if already elevated).
- Prefer denosumab if bisphosphonates are not safe.

***Recommendation**: patients with severe symptoms or calcium levels >14 mg/dL (3,5 mmol/L) will likely require admission for additional treatment. Consider admission to a higher level of care in patients with evidence of cardiac or neurological impairment.*

Follow-up and safety

Reassess calcium (every 6–12 hours and then daily until stabilized).

- Monitor creatinine, potassium, magnesium, phosphate, and signs of rebound hypocalcemia after antiresorptive therapy.
- Prevent nephrotoxicity (avoid NSAIDs, adjust infusions).
- Discharge education: encourage oral hydration, review medications, establish etiological plan (PTH/PTHrP/Vitamin D), and arrange referral.
- Patient disposition in hypercalcemia will depend mainly on corrected serum calcium levels and symptoms.
- Asymptomatic patients with calcium levels <12 mg/dL (3 mmol/L) can generally be safely discharged with outpatient follow-up.

Mini-algorithm (quick reference)

1. ABC + monitoring + confirm corrected/ionized calcium.
2. Hydration (bolus → 200–300 mL/h; target 2 L/day).
3. Calcitonin (bridge therapy) if moderate–severe/symptomatic.
4. IV antiresorptive (zoledronic acid/pamidronate/ibandronate).
5. +/- Corticosteroids if vitamin D–mediated/lymphoma/sarcoidosis.
6. Causes and medications (discontinue thiazides/lithium/vitamin A/D).
7. Dialysis if refractory or CKD with severe symptoms.

Perspectives

Patients with mild symptoms and calcium levels of 12–14 mg/dL (3–3,5 mmol/L) may be discharged after hydration if their symptoms are well controlled, there is no cardiac or neurological impairment, renal function is normal, and the cause is not due to malignancy; otherwise, hospitalization may be required. In patients with malignancy, consultation with oncology is recommended.

Epidemiology

Hypercalcemia is a relatively uncommon metabolic disorder in the general population, with an estimated prevalence between 1 % and 2 %. However, its incidence rises significantly in the hospital setting, where a prevalence of about 4,7 % has been reported.

In patients with malignant disease, hypercalcemia is a common complication, with lifetime prevalence that may exceed 30 % depending on the type of tumor. In the United States and Europe, the neoplasms most frequently associated with hypercalcemia are lung carcinoma, breast carcinoma, and multiple myeloma, which account for a large percentage of malignant hypercalcemia cases.

From an etiological standpoint, approximately 80 % to 90 % of cases are due to two main causes: primary hyperparathyroidism and hypercalcemia secondary to malignant neoplasms. In the general population, primary hyperparathyroidism predominates, whereas in hospitalized or oncology patients, the most frequent cause is malignant hypercalcemia.

In the pediatric population, hypercalcemia is much less common. Even among children with cancer, prevalence rarely exceeds 1,3 %, suggesting protective pathophysiological mechanisms against calcium imbalance.

Regarding prognosis, malignant hypercalcemia is associated with high morbidity and mortality. Hospital mortality is estimated at 6,8 %, and overall 30-day mortality is around 50 % in hospitalized cancer patients who develop this disorder, underscoring its value as a marker of poor oncologic prognosis.

Pathophysiology

Total body calcium is distributed across three main compartments: bone, intracellular, and extracellular. Approximately 99 % of total calcium is found in the skeleton, forming part of the mineral matrix as hydroxyapatite. Of the remaining 1 % present in the extracellular space, about half exists in ionized form, which is biologically active, while the other half is bound to plasma proteins (primarily albumin) or associated with inorganic anions such as phosphate and citrate.

Serum calcium concentration is maintained within a narrow range through the coordinated action of parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (calcitriol), and, to a lesser extent, calcitonin. PTH is secreted in response to decreased serum calcium and raises its concentration through three mechanisms:

- Stimulates bone resorption by activating osteoclasts, releasing calcium and phosphate.
- Increases renal tubular reabsorption of calcium while simultaneously decreasing phosphate reabsorption, thereby favoring the preservation of serum calcium.
- Stimulates calcitriol synthesis in the kidney, which enhances intestinal absorption of calcium and phosphate.

Elevated serum calcium levels, in turn, exert negative feedback on PTH secretion, maintaining mineral homeostasis.

Under normal conditions, calcitriol enhances intestinal absorption of calcium and phosphate, while calcitonin, released by the C cells of the thyroid gland, acts transiently to inhibit bone resorption and promote renal calcium excretion.

Hypercalcemia due to hyperparathyroidism and malignancy

In clinical practice, most cases of hypercalcemia are attributable to two entities: primary hyperparathyroidism and hypercalcemia associated with malignant neoplasms, which together account for approximately 80–90 % of cases. In the general population, primary hyperparathyroidism is the most frequent cause, whereas in hospitalized or oncology patients,

malignant hypercalcemia predominates.

Mechanisms of malignant hypercalcemia

Hypercalcemia of neoplastic origin can develop through three main pathophysiological mechanisms:

1. Tumor secretion of parathyroid hormone–related protein (PTHrP): this is the most common mechanism. It occurs in squamous cell carcinomas of the lung, head and neck, in urothelial tumors, and in breast cancer. PTHrP binds to the same receptor as PTH, producing similar effects: increased bone resorption and renal calcium reabsorption, with suppression of endogenous PTH.
2. Bone metastases with local osteolysis: seen mainly in multiple myeloma and breast carcinoma, where tumor cells release cytokines (IL-1, IL-6, TNF-α, and RANK-L) that stimulate osteoclastic activity and suppress bone formation. This process leads to sustained release of calcium into the circulation.
3. Increased calcitriol ($1,25[OH]_2D$) synthesis: characteristic of lymphomas and other hematologic malignancies, in which malignant cells express extrarenal 1α-hydroxylase, resulting in overproduction of calcitriol and enhanced intestinal absorption of calcium.

In multiple myeloma

Multiple myeloma is one of the most frequent causes of malignant hypercalcemia. It is characterized by the monoclonal proliferation of plasma cells in the bone marrow, which disrupts the balance between bone formation and resorption. Malignant cells increase osteoclast-mediated bone degradation and suppress osteoblastic activity, resulting in continuous release of calcium into the extracellular space.

The outcome is a combination of hypercalcemia, renal insufficiency, anemia, and lytic bone lesions, known as the CRAB syndrome (*Calcium elevation*, Renal failure, Anemia, Bone lesions), which clinically defines the disease. In some cases, hypercalcemia may be the first clinical sign of multiple myeloma, so its detection mandates a complete hematologic evaluation.

Other relevant causes

In addition to the mentioned etiologies, there are multiple conditions capable of altering serum calcium balance:

- Dehydration, which transiently increases plasma calcium concentration.
- Medications such as thiazide diuretics, lithium, and vitamin D or A supplements, which promote renal reabsorption or intestinal absorption of calcium.
- Milk-alkali syndrome, due to excessive intake of calcium carbonate.
- Granulomatous diseases, such as sarcoidosis or tuberculosis, which increase extrarenal calcitriol synthesis.
- Prolonged immobilization, leading to increased bone resorption.
- Rhabdomyolysis, in late phases, due to release and redistribution of calcium.

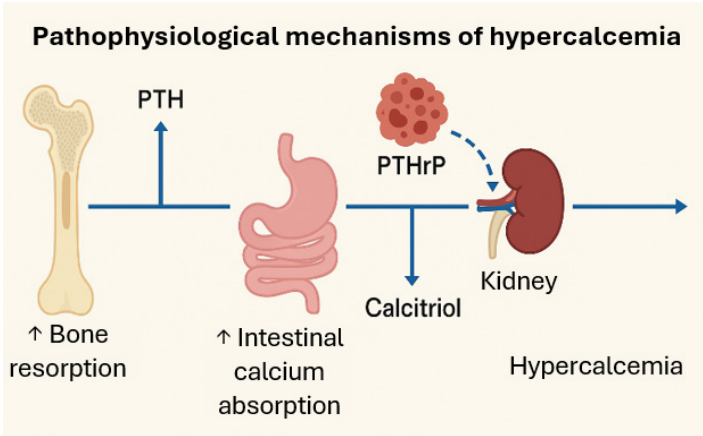

Figure 6.2. Pathophysiological mechanisms of hypercalcemia

Overview of laboratory findings, symptoms, and initial treatment

Hypercalcemia may present with nonspecific or gradually progressive symptoms. Clinical interpretation should be based on an appropriate correlation between the patient's medical history, biochemical findings, and electrocardiographic results, in order to guide the etiology and define the severity of the condition.

Radiographic evaluation

When the cause of hypercalcemia is not evident, chest radiography (CXR) serves as a valuable initial diagnostic tool. This study may reveal signs of primary or metastatic lung neoplasia, or evidence of underlying granulomatous disease such as sarcoidosis or tuberculosis, both recognized causes of hypercalcemia mediated by increased extrarenal calcitriol synthesis.

Laboratory evaluation

Biochemical analysis constitutes the basis for confirming the diagnosis and guiding the pathophysiological origin of the disorder. The study should include, at minimum total serum calcium and ionized calcium. Total calcium represents the sum of free calcium and calcium bound to proteins, primarily albumin. However, only ionized calcium is physiologically active, as it directly participates in neuromuscular excitability and myocardial contraction.

Clinical importance

In the presence of hypoalbuminemia, total calcium may falsely decrease without the existence of true hypocalcemia. Therefore, it is recommended to calculate corrected calcium to obtain a more accurate estimate of free calcium.

Calcium correction for hypoalbuminemia

$$Corrected\ Ca\ (mg/dL) = Measured\ Ca + 0.8 \times (4.0 - Albumin\ [g/dL])$$

This value provides a closer approximation to physiologically available calcium.

- Ionized calcium: Its direct measurement offers a more accurate assessment of active calcium, particularly useful in critically ill patients or those with acid-base disturbances.
- Parathyroid hormone (PTH). PTH is the starting point for etiological evaluation:
  - Elevated PTH: suggests primary or tertiary hyperparathyroidism.

- Suppressed PTH: points to malignant, pharmacologic, or granulomatous causes.

- Vitamin D (25 OH and 1,25 $(OH)_2D$): In cases with normal or low PTH, measurement of vitamin D metabolites helps rule out toxicity from supplementation or increased extrarenal synthesis, as occurs in sarcoidosis, lymphomas, or tuberculosis.

Quick differential diagnosis according to PTH and vitamin D

Table 6.1. Quick differential diagnosis according to PTH and vitamin D

PTH	Vitamin D (25-OH and 1,25-OH_2)	Possible main cause
High	Normal	Primary / tertiary hyperparathyroidism
Low	High	Sarcoidosis, lymphoma, tuberculosis
Low	Normal	Malignant hypercalcemia (PTHrP), immobilization, thiazides
Normal or low	Elevated 25(OH)D	Vitamin D supplementation intoxication

Source: Own elaboration

Electrocardiographic findings

The electrocardiogram (ECG) is an essential tool for detecting the effects of hypercalcemia on cardiac conduction.

The most characteristic finding is shortening of the QT interval, due to reduced ventricular repolarization phase.

In severe cases, more serious abnormalities may occur, such as:

- Atrioventricular blocks.
- Ventricular arrhythmias.
- ST-segment depression or T-wave flattening.

Clinical importance

Electrocardiographic abnormalities are proportional to the degree of calcium elevation and serve as an urgent guide for assessing the need for intensive treatment.

Table 6.2. Electrocardiographic findings

Degree of hipercalcemia	Most frequent ECG finding	Potential complication
Mild (10,5–12 mg/dL)	Slightly shortened QT	No severe abnormalities
Moderate (12–14 mg/dL)	Short QT, ST depression	Risk of supraventricular arrhythmias
Severe (>14 mg/dL)	Very short QT, AV block, ventricular fibrillation	Cardiac arrest, medical emergency

Source: Own elaboration

Pathophysiological synthesis

Taken together, laboratory and ECG findings allow the establishment of a direct relationship between serum calcium levels, PTH and vitamin D activity, and cardiovascular functional impact.

Early recognition of these alterations is essential to initiate appropriate treatment, which is based on vigorous rehydration, inhibition of bone resorption, and specific management according to the cause (hyperparathyroidism, neoplasia, intoxication, or granulomatous disease).

Table 6.3. Pathophysiological synthesis

Category	Parameter / Finding	Clinical interpretation	Comment
Diagnosis confirmation	Total serum calcium	>10,5 mg/dL or >2,6 mmol/L	Increases with plasma proteins; must be corrected for albumin.
	Corrected calcium (mg/dL)	Ca_corrected = Ca_measured + 0,8 × (4 - albumin [g/dL])	Improves accuracy in hypoalbuminemia.
	Ionized calcium	>1,32 mmol/L	Directly measures physiologically active calcium.
Parathyroid hormone (PTH)	Elevated or inappropriately normal	→ Primary or tertiary hyperparathyroidism.	Most frequent cause in outpatient population.
	Supressed	→ Non-parathyroid hypercalcemia (neoplasia, vitamin D, drugs).	Suggests PTHrP production or extrarenal vitamin D activation.
Vitamin D metabolites	Elevated 25(OH)D	Intoxication by vitamin D supplementation.	Review chronic use of high doses or vitamin preparations.
	Elevated $1,25(OH)_2D$	Sarcoidosis, tuberculosis, or lymphoma.	Increased extrarenal calcitriol synthesis.
Other biochemical markers	Low phosphate	Elevated PTH or PTHrP → renal phosphate loss.	Supports parathyroid or paraneoplastic origin.
	High phosphate	Vitamin D or immobilization causes.	Reflects increased intestinal absorption or bone release.
	Elevated creatinine	Dehydration or secondary nephrocalcinosis.	Requires volume correction before antiresorptive therapy.
Imaging studies	Chest radiography (CXR)	Pulmonary nodule, hilar adenopathy, or cavitation.	Suspect neoplasia or sarcoidosis.
	Neck ultrasound	Parathyroid nodule or adenoma.	Confirmation of hyperparathyroidism.
Electrocardiographic findings	Shortened QT	Common; correlates with calcium level.	Due to abbreviated ventricular repolarization.
	AV blocks / Ventricular arrhythmias	In severe hypercalcemia (>14 mg/dL).	Require immediate monitoring and management.
	Flattened T waves or ST depression	Less frequent manifestations.	May be mistaken for ischemia.

Source: Own elaboration

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