Egypt. J. Chem. **Vol.** 68, SI: Z. M. Nofal, pp. 1185- 1194(2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Hypercalcemia: A Metabolic Disorder with Wide Range of Side Effects-An Updated Review for Healthcare Professionals

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Abstract

Background: Hypercalcemia is a prevalent biochemical abnormality with heterogeneous etiologies and system-wide consequences. Its clinical impact spans incidental laboratory findings to life-threatening cardiovascular and neurologic instability.

Aim: To provide an updated, practical synthesis for healthcare professionals covering pathophysiology, epidemiology, diagnostic pathways, management options, and team-based care of hypercalcemia.

Methods: Narrative review of established concepts summarized into a clinician-oriented framework, emphasizing the parathyroid hormone (PTH) decision node, severity grading, targeted investigations, and evidence-based treatments, with attention to patient education and follow-up.

Results: Calcium homeostasis is governed primarily by PTH and vitamin D, with calcitonin as a minor counter-regulator in adults. Most cases derive from primary hyperparathyroidism or malignancy. Severity stratification (mild 10.5–11.9 mg/dL; moderate 12.0–13.9 mg/dL; crisis 14.0–16.0 mg/dL) guides urgency. A suppressed versus inappropriately normal/elevated PTH separates PTH-independent from PTH-mediated causes, prompting tests such as 24-hour urinary calcium, vitamin D metabolites, PTH-related peptide, serum and urine electrophoresis, thyroid studies, metanephrines, and imaging for malignancy or parathyroid disease. Initial treatment prioritizes volume repletion, electrolyte correction, and rapid calcium lowering with calcitonin, followed by durable antiresorptives (zoledronic acid, pamidronate, or denosumab). Etiology-specific measures include parathyroidectomy for eligible primary hyperparathyroidism, glucocorticoids for calcitriol-mediated disease, cinacalcet when surgery is unsuitable, and dialysis for severe, refractory cases. Interdisciplinary follow-up mitigates recurrence and complications.

Conclusion: Etiology-directed, severity-informed care anchored to the PTH decision point enables efficient management that improves safety, reduces recurrence, and aligns with patient goals.

Keywords: hypercalcemia; primary hyperparathyroidism; malignancy-related hypercalcemia; parathyroid hormone; vitamin D; evaluation; calcitonin; bisphosphonates; denosumab; parathyroidectomy; patient education; multidisciplinary care..

1. Introduction

Calcium is the most prevalent cation in the human organism and is indispensable for a wide spectrum of physiological processes, including synaptic transmission, modulation of enzymatic pathways, contractile performance of the myocardium, hemostatic coagulation, and numerous other cellular activities. The overwhelming majority of the body's calcium resides within the skeleton, where it is incorporated into calcium phosphate crystals that impart structural rigidity and serve as a dynamic mineral reservoir. In contrast, only a small proportion is distributed within soft tissues and the extracellular compartment, yet this comparatively minor fraction is tightly regulated because it directly underpins moment-to-moment cellular function. Within the circulation, calcium is partitioned into three principal fractions that together constitute the "total" serum calcium concentration. Approximately 45% is bound to plasma proteins—predominantly albumin—with a lesser contribution from globulins; another ~45% exists as free (ionized) calcium, the physiologically active moiety that interacts with cellular receptors and channels; and the remaining ~10% is complexed with diffusible anions such as bicarbonate, citrate, and phosphate. This tripartite distribution is clinically consequential: whereas total calcium offers a convenient summary measure, it can obscure clinically relevant variation in the ionized fraction, which is the determinant of neuromuscular excitability, secretory responses, and coagulation cascade efficiency [1][2][3].

Reference intervals for total serum calcium typically fall near 8.9–10.1 mg/dL, although modest inter-laboratory differences are common due to methodological variation, calibration standards, and population sampling. Interpretation of a measured value must therefore be anchored to the specific laboratory's stated range. Moreover, total calcium is highly sensitive to the concentration of albumin, given that nearly half of circulating calcium is protein-bound. Hypoalbuminemia, for example, can artifactually depress total calcium despite preservation of ionized calcium, whereas hyperalbuminemia can elevate total calcium without a true increase in the biologically active fraction. In routine practice, clinicians may either adjust

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Receive Date: 22 July 2025, Revise Date: 17 September 2025, Accept Date: 02 October 2025
DOI: 10.21608/ejchem.2025.406530.12082

the total calcium for albumin or, when clinical decisions hinge on precision, directly measure ionized calcium to avoid confounding. Acid–base status exerts an additional, immediate influence on calcium speciation because hydrogen ions compete with calcium for binding sites on albumin. In acidosis, the higher abundance of hydrogen ions increasingly occupies albumin's negatively charged binding pockets, thereby displacing calcium and augmenting the free (ionized) fraction. Conversely, in alkalosis, diminished hydrogen ion availability leaves more binding sites accessible for calcium, which enhances protein binding and reduces the ionized pool. These pH-dependent shifts can materially alter neuromuscular and cardiac physiology even when total calcium appears within reference limits. Clinically, this explains why patients experiencing acute respiratory alkalosis may manifest signs consistent with functional hypocalcemia (e.g., paresthesias, carpopedal spasm) despite a "normal" total calcium, while acidotic states may transiently increase ionized calcium and mitigate such symptoms [1].

Given these interdependencies, sound assessment of calcium homeostasis must consider both albumin concentration and systemic pH. Correcting total calcium for albumin helps approximate the ionized fraction under stable acid–base conditions; however, in settings characterized by rapid pH fluctuations—critical illness, ventilatory disturbances, or perioperative shifts—direct ionized calcium measurement is preferable. Ultimately, a comprehensive evaluation integrates the laboratory's reference range, the distribution of calcium among protein-bound, complex, and ionized states, and the patient's biochemical milieu. In sum, while total calcium remains a useful screening metric, accurate clinical interpretation requires explicit adjustment for albumin and recognition of acid–base effects on protein binding, as increases in hydrogen ion concentration during acidosis occupy albumin binding sites and elevate free calcium, whereas alkalosis has the opposite effect. Thus, calcium levels should also be adjusted for serum pH.[1]

Etiology

The causes of hypercalcemia are commonly conceptualized within two overarching mechanistic frameworks: parathyroid hormone (PTH)–mediated processes and those independent of PTH. This dichotomy is clinically practical because it aligns diagnostic pathways with dominant biochemical signals and helps prioritize testing, imaging, and therapeutic strategies. PTH-mediated hypercalcemia arises when inappropriate PTH secretion or action elevates serum calcium, whereas non–PTH-mediated forms reflect alternative drivers—renal tubular handling of calcium, vitamin D excess, skeletal turnover, malignancy-associated factors, medications, or endocrine comorbidities—that increase calcium independent of primary parathyroid stimulation. Appreciating these categories, and their finer-grained subtypes, supports accurate differentiation among etiologies that can otherwise present with overlapping biochemical and clinical profiles [2].

Parathyroid Hormone–Mediated

Primary hyperparathyroidism. Primary hyperparathyroidism (PHPT) is defined by elevated serum calcium in the setting of frankly elevated or inappropriately normal PTH concentrations—"inappropriate" because physiologically normal PTH should be suppressed in hypercalcemic states. The archetypal lesion is a solitary parathyroid adenoma, though hyperplasia or multi-gland disease may also occur. Clinically, PHPT often comes to light through routine biochemical screening, with many patients displaying high-normal or only modestly increased calcium and minimal symptoms. Nonetheless, the sustained catabolic skeletal effects of excess PTH—enhanced osteoclastic bone resorption and cortical bone loss—can culminate in osteoporosis and fragility fractures. Renal sequelae are similarly prominent: hypercalciuria predisposes to nephrolithiasis, and long-standing mineral derangements may impair renal function and, in severe cases, precipitate renal failure. On occasion, particularly with very high PTH output, patients may present with marked hypercalcemia and its systemic manifestations, underscoring the wide phenotypic spectrum of PHPT [2].

Tertiary hyperparathyroidism. Tertiary hyperparathyroidism represents the evolution of chronic secondary hyperparathyroidism into autonomous glandular hyperfunction. Here, persistent hypocalcemic stimuli—most notably the phosphate retention and vitamin D dysregulation of advanced chronic kidney disease—provoke diffuse parathyroid hyperplasia. Over time, the glands become relatively independent of the original stimulus, secreting high amounts of PTH even after the underlying renal milieu improves, including after kidney transplantation. Biochemically, tertiary disease is characterized by concomitantly elevated calcium and PTH, mirroring the laboratory profile of PHPT but with a distinct pathophysiologic trajectory rooted in chronic overstimulation and resultant hyperplasia [3].

Familial hypocalciuric hypercalcemia. Familial hypocalciuric hypercalcemia (FHH) is an inherited disorder arising from loss-of-function variants in the calcium-sensing receptor (CaSR) gene. Because CaSR is integral to systemic calcium homeostasis—modulating PTH secretion in the parathyroid glands and calcium reabsorption in the kidney—its reduced sensitivity shifts the set point at which the body perceives calcium as "normal." The consequence is mild-to-moderate hypercalcemia and nonsuppressed PTH levels that can resemble PHPT. The crucial discriminant is renal handling: impaired CaSR signaling in the thick ascending limb and distal nephron augments tubular calcium reabsorption, producing characteristically low urinary calcium excretion (hypocalciuria). This biochemical signature, rather than the degree of hypercalcemia alone, is often decisive in distinguishing FHH from other PTH-mediated states [4].

Medication-related PTH modulation. Several agents can provoke PTH-mediated hypercalcemia by altering the regulation or actions of the hormone. Lithium, for example, increases the calcium threshold for PTH suppression, effectively raising the "set point" and thereby sustaining higher serum calcium before negative feedback curtails PTH secretion. Clinically, this manifests as hypercalcemia with relatively preserved or elevated PTH among long-term lithium users [5]. Anabolic osteoporosis therapies that signal through the PTH/PTH-related peptide (PTHrP) pathway may also transiently increase serum calcium. Teriparatide, a recombinant human PTH (1–34) analog, can produce short-lived post-dosing hypercalcemia as part of its pharmacodynamic profile [6]. Abaloparatide, a synthetic analog of PTHrP that binds PTH receptor type 1 with distinct receptor kinetics, similarly potentiates PTH/PTHrP actions and can increase circulating calcium, particularly in the hours following administration [7].

Non–Parathyroid Hormone–Mediated

Medication-induced mechanisms. Several commonly used medications elevate calcium through PTH-independent pathways. Thiazide diuretics enhance calcium reabsorption in the distal convoluted tubule by upregulating transcellular transport mechanisms. In parallel, their inhibition of the sodium–chloride cotransporter reduces intravascular volume, which secondarily promotes proximal sodium and water reabsorption and can increase passive calcium uptake, collectively driving a PTH-independent rise in serum calcium [5]. Excess ingestion of calcium carbonate—often undertaken for dyspepsia or reflux symptoms—can precipitate the classic milk-alkali syndrome. The triad of hypercalcemia, metabolic alkalosis, and renal dysfunction reflects the combined effects of alkali load, decreased glomerular filtration with reduced calcium clearance, and volume contraction, with potential for substantial morbidity if unrecognized [8]. In addition, prolonged administration of retinoic acid augments osteoclastic activity and skeletal resorption, tipping the balance of bone remodeling toward net calcium release into the circulation [9].

Hypercalcemia of malignancy. Malignancy-associated hypercalcemia is a frequent and clinically urgent entity with heterogeneous mechanisms. The most prevalent pathway involves tumor overexpression of PTHrP, which, owing to structural homology with PTH at the receptor-binding domain, engages PTH receptors on bone and kidney to stimulate osteoclastic bone resorption and renal calcium conservation. This "humoral" hypercalcemia can occur in diverse solid tumors and often progresses rapidly. A second mechanism entails direct skeletal involvement: bone metastases from cancers such as breast, lung, or renal malignancies create a local microenvironment rich in osteoclast-activating factors, accelerating bone breakdown and liberating calcium. A third pathway arises from dysregulated vitamin D metabolism; certain hematologic malignancies—notably Hodgkin and non-Hodgkin lymphomas—and granulomatous diseases such as sarcoidosis and tuberculosis express extrarenal 1α-hydroxylase, increasing conversion of 25-hydroxyvitamin D to its active 1,25-dihydroxy form. The resultant enhancement of intestinal calcium absorption and bone resorption contributes further to hypercalcemia. For an expanded discussion of diagnostic strategies and management nuances in this domain, see StatPearls' companion article "Malignancy-Related Hypercalcemia" [10][11].

Excess Vitamin D. Beyond the calcitriol-mediated mechanism described above, elevation of 25-hydroxyvitamin D itself is a recognized driver of hypercalcemia. Exogenous sources predominate high-dose supplementation—intentional or inadvertent—and overconsumption of vitamin D–fortified foods can elevate circulating 25-hydroxyvitamin D to levels that enhance intestinal calcium absorption and mobilize skeletal calcium stores. The concomitant intake of calcium-containing dairy or supplements can amplify the hypercalcemic effect, emphasizing the importance of a careful nutritional and pharmacologic history in the assessment of elevated calcium [*no new citation added; preserves original context*].

Endocrinopathies. Several endocrine disorders influence calcium homeostasis through effects on bone turnover, renal clearance, or hormone cross-talk. In hyperthyroidism, thyroid hormone excess accelerates bone remodeling and preferentially stimulates osteoclastic resorption, shifting mineral balance toward calcium release. Consequently, both total and ionized calcium may be increased, even when overall bone density is compromised by the catabolic milieu [12]. Pheochromocytoma can be associated with hypercalcemia through two distinct routes: first, as a component of multiple endocrine neoplasia type 2 (MEN2), in which primary hyperparathyroidism coexists; second, in a phenotype resembling humoral malignancy-related hypercalcemia, where tumor-related factors, including PTHrP, promote calcium elevation independent of parathyroid pathology [13]. Adrenal insufficiency represents a less common endocrine precipitant. Volume depletion in this condition leads to reduced glomerular filtration and augmented proximal tubular reabsorption, thereby decreasing renal calcium excretion. Additional contributions may stem from alterations in vitamin D metabolism, including potential increases in 1,25-dihydroxyvitamin D, though the precise biochemical mechanisms remain incompletely delineated [14].

Immobilization-related hypercalcemia. Prolonged immobilization, while an uncommon cause overall, is salient in populations with markedly reduced mobility—such as individuals with spinal cord injury, advanced neuromuscular disease, or extended bed rest. Mechanical unloading diminishes osteoblastic bone formation and favors osteoclast-mediated resorption, resulting in a net efflux of calcium from the skeleton into the bloodstream. This imbalance can manifest as hypercalcemia days to weeks after the onset of immobility and may be exacerbated by concurrent risk factors, including high bone turnover states or recent fractures [15]. **Other rare causes.** A variety of additional, infrequent etiologies have been documented in case reports and small series. While individually uncommon, these reports broaden the differential diagnosis and underscore the need for a thorough clinical history, judicious laboratory evaluation, and attention to context when hypercalcemia is discovered [16].

In summary, organizing the differential diagnosis of hypercalcemia into PTH-mediated and non–PTH-mediated categories provides a pragmatic scaffold for evaluation. Within the PTH-mediated group, primary and tertiary hyperparathyroidism and select medication effects (e.g., lithium, PTH/PTHrP analogs) dominate. The non–PTH-mediated cohort encompasses drug-induced alterations in renal or skeletal handling of calcium, malignancy-driven humoral or skeletal mechanisms, vitamin D excess, endocrine comorbidities, immobilization, and rarer entities described in the literature. Careful alignment of clinical features with biochemical patterns—particularly PTH levels, urinary calcium excretion, vitamin D metabolites, and medication exposures—guides precise attribution of cause and informs targeted therapy across this diverse etiologic spectrum [2][3][4][5][6][7][5][8][9][10][11][12][13][14][15][16].

Epidemiology

Hypercalcemia is relatively uncommon at the population level yet represents a frequent biochemical abnormality in clinical practice. Population-based estimates place its prevalence at roughly 1% to 2%, a range that underscores both its general rarity and the need for targeted case-finding in at-risk groups. Etiologically, the burden is highly concentrated: approximately 90% of cases arise from either primary hyperparathyroidism or malignancy-associated hypercalcemia, reflecting two dominant and Pathophysiologically distinct pathways—excess parathyroid hormone secretion versus tumor-driven dysregulation of calcium homeostasis. Within the community, primary hyperparathyroidism exhibits a point prevalence between 0.2% and 0.8%, with rates rising progressively with advancing age, consistent with the cumulative likelihood of parathyroid adenomatous change and age-related shifts in calcium–vitamin D physiology. By contrast, across oncology populations, about 2% of all cancers are complicated by hypercalcemia, highlighting the syndrome's importance as a paraneoplastic or skeletal-metastatic manifestation. Age stratification further refines this picture: in pediatric cohorts, hypercalcemia is distinctly less common, with reported prevalence spanning approximately 0.4% to 1.3%, a pattern that mirrors the lower incidence of both primary hyperparathyroidism and the malignancies most often implicated in calcium dysregulation among children. Taken together, these figures delineate a clear epidemiologic profile—overall low prevalence, strong etiologic concentration in two categories, upward age gradients for primary hyperparathyroidism, and comparatively infrequent occurrence in childhood—thereby informing diagnostic vigilance and resource allocation across primary care, endocrinology, and oncology settings [17].

Pathophysiology

In adult physiology, fine control of extracellular calcium concentration is orchestrated predominantly by parathyroid hormone (PTH) and vitamin D, which operate in a tightly coupled endocrine axis to stabilize minute-to-minute and day-to-day calcium fluxes across bone, kidney, and intestine. When serum calcium falls, PTH secretion rises and acts rapidly to restore normocalcemia. At the skeleton, PTH promotes bone resorption, thereby mobilizing mineral stores and releasing calcium into the circulation. In the kidney, PTH enhances tubular calcium reabsorption, limiting urinary calcium losses, and simultaneously stimulates the activity of 1-α-hydroxylase, the mitochondrial enzyme that converts 25-hydroxy-vitamin D to its hormonally active form, 1,25-dihydroxy-vitamin D (calcitriol). Calcitriol, in turn, augments intestinal calcium uptake—principally in the small bowel—by increasing the expression and activity of epithelial transport proteins and cytosolic binding partners, thereby increasing the efficiency with which dietary calcium enters the bloodstream. Through these coordinated actions, the PTH–vitamin D axis raises serum calcium and reestablishes homeostasis following hypocalcemic perturbations [18].

Although less central in adults, calcitonin provides an additional, counter-regulatory influence that becomes most apparent in states of acute calcium excess or in specific developmental contexts. Secreted by thyroidal parafollicular (C) cells in response to elevations in serum calcium, calcitonin lowers circulating calcium by several complementary mechanisms: it fosters mineral deposition within bone and attenuates osteoclastic bone resorption; it diminishes renal tubular reclamation of calcium, thereby increasing urinary calcium excretion; and it can reduce net gastrointestinal absorption of calcium. Collectively, these effects favor a downward adjustment of serum calcium concentration. In mature adults, however, calcitonin's role in steady-state calcium regulation is relatively minor compared with the dominant PTH–vitamin D system. By contrast, during childhood—when skeletal modeling and mineral accrual are especially active—calcitonin serves as a more prominent physiologic modulator of calcium balance. This developmental distinction helps explain why pharmacologic calcitonin exerts modest chronic effects in adults yet retains relevance in pediatric physiology and in selected acute clinical scenarios characterized by brisk calcium shifts [19].

History and Physical

Hypercalcemia is frequently discovered incidentally during routine biochemical testing obtained for unrelated clinical indications. Symptomatology tends to emerge as serum calcium rises substantially, and particularly when concentrations exceed approximately 12 mg/dL. At that threshold, patients commonly report polyuria and polydipsia (reflecting impaired urinary concentrating ability), constipation, generalized weakness, nausea, vomiting, fatigue, anorexia, and varying degrees of cognitive or affective disturbance, including confusion and other neuropsychiatric changes. These manifestations stem from several convergent mechanisms: depression of neuronal excitability and synaptic transmission; renal tubular dysfunction with water loss and volume depletion; and direct effects of calcium on central nervous system function. Cardiac tissues are similarly dependent on tightly regulated calcium fluxes. Excess calcium alters electrophysiologic properties and conduction, producing characteristic electrocardiographic (ECG) changes—most notably QT-interval shortening, PR-interval prolongation, and QRS widening (see Image: ECG Findings of Hypercalcemia). Clinically, these disturbances may present as bradycardia, varying degrees of atrioventricular block, and other arrhythmias, any of which can be hemodynamically significant or life-threatening. With more extreme elevations, encephalopathy may progress to stupor or coma. Chronic hypercalcemia carries additional risks. Precipitation of calcium salts in the urinary tract promotes nephrolithiasis; sustained pancreatic injury can culminate in pancreatitis; and increased gastric acid exposure contributes to peptic ulcer disease. When hypercalcemia is driven by primary hyperparathyroidism, skeletal consequences are prominent: osteoclast-mediated bone resorption leads to osteopenia and osteoporosis, with an attendant rise in fragility fractures. Clinicians often summarize the multisystem burden of the disorder with the mnemonic "groans, bones, stones, moans, thrones, and psychiatric overtones," which captures gastrointestinal discomfort, skeletal pain and fractures, renal stones, diffuse aches and mood changes, polyuria with urinary urgency, and neuropsychiatric symptoms. Together, these historical features—ranging from subtle fatigue to acute neurologic and cardiac instability—provide crucial context for interpreting a laboratory-detected elevation in serum calcium and gauging the acuity and severity of the disorder [20].

Physical Examination

The physical examination may be unremarkable, especially in mild or subacute disease, and a normal examination does not exclude clinically meaningful hypercalcemia. Nonetheless, specific abnormalities can be elicited and should be actively sought. Cardiovascular assessment may reveal bradycardia or irregular rhythms through pulse palpation or auscultation that correspond to ECG conduction abnormalities. Neurologically, diminished deep tendon reflexes are not uncommon, reflecting depressed neuromuscular excitability. A focused musculoskeletal evaluation can demonstrate reduced muscle tone and diffuse myalgias or tenderness, aligning with patients' reports of weakness and generalized discomfort. Additional findings may point toward the underlying cause—for example, clues of volume depletion in those with substantial polyuria or disease-specific stigmata related to endocrine, malignant, or granulomatous etiologies, though such signs are variable and often nonspecific. In aggregate, careful examination complements the history by highlighting the systemic reach of hypercalcemia, identifying immediate complications (particularly arrhythmias and volume status derangements), and narrowing the differential diagnosis when considered alongside biochemical data and ECG evaluation.

Evaluation

Hypercalcemia is most often identified incidentally on routine biochemical panels obtained for unrelated reasons. Once an elevated serum calcium is confirmed, the severity should be stratified because of clinical risk and urgency scale with the degree of elevation. Conventionally, mild hypercalcemia is defined as 10.5 to 11.9 mg/dL, moderate hypercalcemia as 12.0 to 13.9 mg/dL, and hypercalcemic crisis as 14.0 to 16.0 mg/dL. This initial classification informs both the tempo of evaluation and the need for immediate therapy. A meticulous clinical history and comprehensive physical examination—paired with a careful review of all prescribed and over-the-counter medications, supplements, and recent dietary changes—are foundational to etiologic determination. The pivotal biochemical branch point is measurement of parathyroid hormone (PTH) to distinguish PTH-mediated PTH-independent hypercalcemia. In many individuals, the cause can be inferred from the constellation of history, examination, and targeted laboratory data; however, additional investigations are sometimes necessary to refine the differential diagnosis. If PTH concentrations are frankly elevated or inappropriately normal (i.e., not suppressed despite hypercalcemia), the disorder is categorized as PTH-mediated. The principal considerations within this pathway are primary hyperparathyroidism, tertiary hyperparathyroidism, and familial hypocalciuric hypercalcemia (FHH). To discriminate among these entities, a 24-hour urinary calcium excretion study is recommended: hyperparathyroidism typically demonstrates elevated urinary calcium, whereas FHH characteristically shows low urinary calcium. Interpreting urinary calcium alongside clinical context (e.g., chronic kidney disease favoring tertiary disease, family history suggesting FHH) sharpens diagnostic accuracy.

Conversely, if PTH levels are suppressed, attention shifts to PTH-independent mechanisms. Important categories include medication effects (e.g., thiazides, vitamin A derivatives), immobilization, occult or known malignancy (humoral or osteolytic mechanisms), granulomatous diseases, and other endocrinopathies. In this arm of the algorithm, ancillary laboratory testing is chosen selectively to match the most plausible etiologies. Useful studies may include ionized calcium (to confirm physiologically active hypercalcemia), phosphorus, magnesium, alkaline phosphatase, 25-hydroxy-vitamin D (nutritional/toxic exposure), estimated glomerular filtration rate (renal handling), parathyroid hormone–related protein (PTHrP) (humoral malignancy), serum and urine protein electrophoresis (plasma cell dyscrasia), thyroid function tests, plasma metanephrines (pheochromocytoma), and insulin-like growth factor 1 where clinically indicated. Test selection should be hypothesis-driven rather than indiscriminate, emphasizing parsimony and diagnostic yield. While biochemical confirmation is straightforward, additional diagnostics refine the etiologic assessment and guide management:

- **Electrocardiogram (ECG):** Hypercalcemia produces characteristic conduction changes, including QT-interval shortening, low-amplitude T waves, ST-segment elevation, PR prolongation, and tall, widened QRS complexes. Rhythm disturbances—such as bradycardia and premature ventricular contractions—may also be evident and, when present, warrant prompt attention.
- **Renal ultrasonography:** Chronic calcium excess predisposes to **nephrolithiasis**; ultrasound provides a noninvasive means to detect stones and evaluate obstructive uropathy.
- **Bone mineral density assessment (DEXA):** In suspected or confirmed primary hyperparathyroidism, DEXA scanning can reveal osteopenia or osteoporosis, particularly at cortical-rich sites, informing fracture risk and the urgency of definitive parathyroid evaluation.
- **Age-appropriate malignancy screening:** When a neoplastic process is suspected, standard screening and diagnostic imaging—mammography, colonoscopy, low-dose lung CT in eligible patients, and abdominal CT or MRI—may uncover the primary tumor or metastatic disease responsible for hypercalcemia.
- **Thyroid/parathyroid imaging:** Neck ultrasonography can localize a parathyroid adenoma or identify glandular hyperplasia. If sonography is nonlocalizing or equivocal, parathyroid nuclear scintigraphy (e.g., sestamibi) or four-dimensional CT provides complementary anatomical and perfusion detail to guide surgical planning.

In aggregate, a structured evaluation proceeds from confirmation and grading of hypercalcemia, through a PTH-anchored decision tree, to targeted laboratory and imaging studies aligned with the leading diagnostic hypotheses. This strategy minimizes unnecessary testing, accelerates etiologic clarification, and ensures that high-risk presentations—particularly hypercalcemic crisis and those with cardiac instability—are recognized and managed without delay.

Table 1. Diagnostic Evaluation of Hypercalcemia

Step	Rationale	Key tests / thresholds	Typical next actions
Confirm and grade calcium	Stratify urgency	Repeat total Ca; consider ionized Ca; classify: mild 10.5–11.9, moderate 12.0–13.9, crisis 14.0–16.0 mg/dL	Initiate urgent management for crisis; ECG if symptomatic
Assess albumin & pH	Interpret total Ca accurately	Serum albumin; blood gas if indicated	Correct for albumin/pH or measure ionized Ca directly
PTH measurement (decision node)	Distinguish PTH-mediated vs non-PTH	Intact PTH	If ↑/inappropriately normal → PTH-mediated; if suppressed → non-PTH
If PTH-mediated	Differentiate PHPT/tertiary vs FHH	24-h urinary Ca (high in hyperparathyroidism, low in FHH); eGFR	Evaluate for CKD/tertiary disease; family history; genetics when needed
If PTH-independent	Identify alternate drivers	25-OH and 1,25-OH_2 vitamin D, PTHrP, SPEP/UPEP, Mg/Phos/ALP, TSH/T4, plasma metanephrines	Tailor to malignancy, granulomatous disease, endocrine causes, drugs, immobilization
Imaging	Define complications/etiology	ECG; renal US; DEXA; age-appropriate cancer screening; neck US ± sestamibi/4D-CT	Manage stones/osteoporosis; localize parathyroid adenoma; stage malignancy

Treatment / Management

The therapeutic approach to hypercalcemia is guided by two principles: the acuity and magnitude of calcium elevation, and the underlying pathophysiologic driver. Broadly, management seeks to (1) enhance elimination of calcium from the extracellular fluid, (2) reduce gastrointestinal absorption, and (3) attenuate skeletal efflux by inhibiting bone resorption. Interventions are therefore layered and tailored—rapid-onset measures stabilize the patient while slower-acting agents provide durable control. Etiology-specific strategies (e.g., parathyroidectomy for primary hyperparathyroidism, glucocorticoids for calcitriol-mediated disease) are integrated once initial stabilization is achieved. Hydration. Volume depletion is common in hypercalcemia due to nephrogenic diabetes insipidus–like physiology and natriuresis, and it perpetuates calcium retention by reducing glomerular filtration. Accordingly, the cornerstone of initial therapy is intravenous isotonic saline to restore intravascular volume and augment calciuresis. A typical practice is to begin 0.9% saline infusion and titrate to achieve adequate urine output and clinical euvolemia, with vigilant reassessment for signs of fluid overload in susceptible patients (e.g., heart failure, advanced kidney disease). By improving renal perfusion and sodium delivery to the distal nephron, hydration alone often produces a clinically meaningful early fall in serum calcium [21].

Electrolyte replacement. Perturbations in potassium, magnesium, and phosphate frequently accompany hypercalcemia and can compound neuromuscular symptoms, blunt therapeutic responses, or predispose to arrhythmias. Hypomagnesemia in particular impairs parathyroid hormone dynamics and can render calcium reduction strategies less effective, while hypokalemia increases arrhythmic risk. Hypophosphatemia reflects and reinforces high bone turnover. Systematic repletion of potassium, magnesium, and phosphate to the normal range is therefore integral to comprehensive management and should proceed in parallel with other treatments, with dosing individualized to renal function and the clinical setting. Calcitonin. For rapid, short-term lowering of calcium—especially in symptomatic moderate-to-severe hypercalcemia—calcitonin provides a useful bridge therapy. Administered intramuscularly or subcutaneously at 4 units/kg every 12 hours, calcitonin begins to reduce serum calcium within approximately 2 hours, offering early symptomatic relief. However, tachyphylaxis typically develops, and the effect wanes after about 4 to 7 days, limiting its role as a chronic therapy. In practice, calcitonin is co-administered with hydration and a longer-acting antiresorptive so that its prompt effect covers the lag before definitive agents take hold [22].

Bisphosphonates. Intravenous bisphosphonates antagonize osteoclast-mediated resorption, thereby addressing the skeletal source of calcium flux. Pamidronate and zoledronic acid are both approved for hypercalcemia of malignancy, with zoledronic acid demonstrating superior efficacy in comparative studies. Their onset is delayed—serum calcium typically normalizes over ~3 days—so they are commonly initiated early, in parallel with saline and calcitonin, to secure sustained control once the latter's effect dissipates. Renal function should be assessed prior to dosing, infusion rates adjusted as indicated, and clinicians should monitor for hypocalcemia after tumor-related drivers abate or in the presence of vitamin D deficiency [23]. Denosumab. In malignancy-associated hypercalcemia, particularly when bisphosphonates are contraindicated or ineffective—denosumab, a monoclonal antibody targeting RANK ligand, serves as a potent antiresorptive. By inhibiting RANKL, denosumab functionally suppresses osteoclast formation and activity, leading to reliable reductions in serum calcium. It is widely regarded as first-line therapy in hypercalcemia of malignancy, often used alongside aggressive hydration and, where appropriate, bisphosphonates. An important advantage is its favorable profile in renal impairment, expanding options for patients with compromised kidney function. As with other antiresorptives, calcium and vitamin D status should be optimized to mitigate rebound hypocalcemia once tumor burden is controlled [23][24].

Parathyroidectomy. For primary hyperparathyroidism, definitive treatment is surgical excision of the hyperfunctioning gland(s) when guideline-based criteria are met. Patients should be evaluated for parathyroidectomy if serum calcium exceeds the upper limit of normal by >1.0 mg/dL, if there is osteoporosis on DEXA, a fragility or vertebral fracture, 24-hour urine calcium >400 mg/d, any history of nephrolithiasis, or age <50 years [25]. In eligible patients, parathyroidectomy offers durable biochemical cure, improves bone density, and reduces renal complications, thereby providing a long-term solution to hypercalcemia that supportive measures alone cannot achieve [26]. Cinacalcet. Cinacalcet (a calcimimetic) is approved for secondary hyperparathyroidism due to renal failure and is also used in primary hyperparathyroidism for patients who are poor surgical candidates or decline surgery. Its mechanism—increasing the sensitivity of calcium-sensing receptors on parathyroid cells—results in suppression of PTH secretion and downstream lowering of serum calcium. More recently, case reports suggest a role for cinacalcet in select instances of hypercalcemia of malignancy, although data remain limited and such use is generally considered adjunctive and individualized [27].

Renal replacement therapy. In severe hypercalcemia complicated by renal failure or when intravenous hydration is contraindicated or poorly tolerated (e.g., refractory heart failure), hemodialysis using a low- or zero-calcium bath can rapidly reduce serum calcium. Dialysis is typically reserved for life-threatening presentations—refractory arrhythmias, neurologic compromise—or when pharmacologic options are unsafe or insufficient. Close monitoring is essential to prevent overly rapid shifts in calcium and to coordinate subsequent maintenance therapy once stability is achieved. Glucocorticoids. When hypercalcemia stems from calcitriol overproduction—classically in lymphoma or granulomatous diseases—glucocorticoids directly address the driver by inhibiting 1-α-hydroxylase activity, thereby lowering calcitriol and attenuating intestinal calcium absorption. A practical regimen is oral prednisone 20–40 mg daily, with dosage and duration adjusted to response and the underlying condition. Concurrent evaluation and treatment of the primary disease process are crucial for sustained control [23].

Agents largely avoided. Several historical therapies have fallen out of favor due to toxicity. Gallium nitrate suppresses osteoclast function akin to bisphosphonates but is associated with nephrotoxicity and additional electrolyte disturbances; it has therefore been withdrawn from the market. Mithramycin rapidly inhibits osteoclast RNA synthesis and can lower calcium, but hepatotoxicity and nephrotoxicity significantly constrain its use. In contemporary practice, these agents are generally avoided in favor of safer, better-studied alternatives. Ketoconazole. As an antifungal, ketoconazole exerts an off-target endocrine effect relevant to specific hypercalcemic states. By inhibiting 1-α-hydroxylase in macrophages, it reduces generation of active vitamin D (calcitriol) and can thereby ameliorate hypercalcemia in disorders marked by extrarenal calcitriol production. Its role is niche and adjunctive, used when first-line measures are insufficient or contraindicated, and requires attention to drug–drug interactions and hepatic safety [28][29].

Treat the underlying disease. Beyond acute correction of calcium, durable control depends on identifying and managing the inciting pathology. This may entail resecting a parathyroid adenoma, instituting cytotoxic or targeted therapy for a malignancy, tapering or substituting a causative medication, treating granulomatous inflammation, optimizing thyroid or adrenal disorders, or implementing mobilization strategies in immobilization-related hypercalcemia. Early collaboration across endocrinology, oncology, nephrology, and surgery streamlines this process and reduces recurrence. In sum, effective management of hypercalcemia combines immediate stabilization (hydration, rapid-onset calcium-lowering agents) with definitive antiresorptive therapy and etiology-directed interventions. Therapy should be individualized to the patient's hemodynamic status, renal function, and causal diagnosis, with close monitoring for electrolyte shifts and cardiac effects throughout the course of care [21][22][23][24][25][26][27][28][29].

Table 2. Therapeutic Options for Hypercalcemia

Therapy/class	Indication/setting	Typical dose/administration	Onset / duration	Notable considerations
Isotonic saline hydration	All symptomatic; volume depletion	0.9% saline IV, titrate to euvolemia/adequate urine output	Hours / persists while infused	Monitor for fluid overload; reassess electrolytes/creatinine
Electrolyte repletion	Concomitant deficits	K^+, Mg^{2+}, PO_4^{3-} per labs/renal function	Hours / variable	Hypomagnesemia impairs response; correct arrhythmia risk
Calcitonin	Rapid, short-term lowering	4 units/kg SC/IM q12h	~2 h / tachyphylaxis by 4–7 d	Bridge while antiresorptives take effect
IV bisphosphonates	Hypercalcemia of malignancy; high bone turnover	Zoledronic acid; or pamidronate, single IV dose	48–72 h / weeks	Check renal function; risk hypocalcemia
Denosumab (anti-RANKL)	Malignancy-related hypercalcemia, esp. renal impairment or bisphosphonate-refractory	SQ per labeling	Days / weeks	Effective in CKD; supplement Ca/Vit D to avoid rebound
Glucocorticoids	Calcitriol-mediated states (lymphoma, granulomatous)	Prednisone 20–40 mg PO daily	Days / while treated	Taper per response; treat underlying disease
Cinacalcet	PHPT not surgical; secondary HPT	Per labeling, titrated	Days / ongoing	Calcimimetic; lowers PTH/Ca
Hemodialysis	Severe, refractory; fluid-intolerant; renal failure	Low/zero-Ca bath	Immediate / hours	For life-threatening cases; coordinate maintenance plan
Adjuncts (e.g., ketoconazole)	Select extrarenal calcitriol excess	As clinically indicated	Variable	Hepatic interactions; niche role

Differential Diagnosis

Although hypercalcemia can manifest with a wide array of complaints, patients most often report features traceable to volume depletion and excess urine output. Accordingly, dehydration and polyuria represent practical starting points for the differential diagnosis, as each may either precipitate or mimic hypercalcemic states and frequently co-occur.

Dehydration

Isolated volume depletion can yield spuriously elevated serum calcium concentrations through hemoconcentration. A careful history typically uncovers reduced fluid intake or increased insensible and renal losses; clinicians should also probe for recent gastrointestinal fluid loss, febrile illness, diuretic exposure, or environmental heat stress. On examination, classic signs of hypovolemia may be present, including xerostomia, dry skin with diminished turgor, tachycardia, orthostatic or absolute hypotension, and oliguria. Because dehydration itself contributes to impaired renal calcium clearance, prompt restoration of intravascular volume is essential. Rehydration—preferably with oral fluids when feasible or intravenous isotonic crystalloids when necessary—both corrects the hemoconcentration artifact and improves glomerular filtration, thereby enhancing calciuresis. Importantly, serum calcium should be reassessed after euvolemia is achieved to distinguish true hypercalcemia from transient concentration effects and to avoid unnecessary downstream testing predicated on an artifactual value.

Polyuria

When excessive urination is the leading complaint, the diagnostic net must broaden beyond calcium disorders. Uncontrolled diabetes mellitus commonly produces polyuria via osmotic diuresis from hyperglycemia; corroborating clues include polydipsia, weight loss, glucosuria, and elevated serum glucose. Diabetes insipidus—central or nephrogenic—causes water diuresis with very dilute urine, often accompanied by hypernatremia and elevated plasma osmolality. Distinguishing these entities hinges on basic laboratory screening (serum and urine osmolality, sodium, and glucose) and, when indicated, formal water deprivation or desmopressin testing. Acute-onset polyuria may also signal intercurrent urinary tract infection, for which urinalysis and urine culture are decisive, or hypokalemia, which impairs renal concentrating ability and should be detected on serum electrolytes. Of note, sustained polyuria—whatever the cause—can itself precipitate dehydration, thereby exacerbating or unmasking hypercalcemia. Thus, evaluation should proceed in parallel: identify and treat the proximate driver of polyuria while concurrently correcting volume status and reassessing calcium once fluid balance is restored.

Prognosis

Outcomes in hypercalcemia are fundamentally contingent upon the underlying etiology and the timeliness of definitive therapy. Many causes are benign or readily reversible and therefore portend a favorable trajectory once addressed. Medication-induced hypercalcemia, for example, typically resolves with dose adjustment or discontinuation of the offending agent. Similarly, primary hyperparathyroidism—though capable of causing skeletal and renal morbidity—has an excellent long-term outlook when treated with curative parathyroidectomy or appropriately monitored when surgery is deferred. By contrast, hypercalcemia arising from malignancy or granulomatous disease often signals advanced or systemic pathology and carries a substantially poorer prognosis. In these contexts, calcium elevation may recur despite initial control, and overall survival largely reflects the course of the primary illness. This divergence in outcomes underscores a central management principle: identifying the cause of hypercalcemia is as critical as correcting the calcium level itself. Etiologic clarity not only guides targeted therapy but also informs counseling, follow-up intensity, and interdisciplinary coordination with oncology, rheumatology, or infectious disease as appropriate.

Complications

Unchecked or recurrent hypercalcemia can involve multiple organ systems and produce a characteristic constellation of complications:

- **Depression:** Mood disturbance and anergia are common, reflecting calcium’s effects on central neurotransmission.
- **Kidney stones:** Hypercalciuria promotes calcium salt precipitation, predisposing to nephrolithiasis and obstructive uropathy.
- **Bone pain:** Enhanced osteoclastic activity and cortical bone loss generate diffuse or focal skeletal discomfort.
- **Constipation:** Reduced gastrointestinal motility is frequent, sometimes accompanied by anorexia and abdominal pain.
- **Pancreatitis:** Calcium-mediated activation of pancreatic enzymes has been implicated in both acute and recurrent pancreatitis.
- **Renal failure:** Vasoconstriction and nephrogenic diabetes insipidus–like physiology impair renal function; prolonged injury may culminate in chronic kidney disease.
- **Gastric ulcers:** Increased gastric acid exposure and mucosal vulnerability contribute to peptic ulcer disease.
- **Paresthesias:** Altered neuromuscular excitability can present as distal tingling or numbness.
- **Syncope and arrhythmias:** Bradyarrhythmias, heart block, and other conduction disturbances may lead to presyncope or frank syncope.
- **Altered mental status:** Cognitive slowing, confusion, and in severe cases stupor or coma can occur, particularly at very high calcium levels.

Timely recognition and correction of serum calcium, coupled with targeted treatment of the underlying disorder, mitigate these risks and improve both short-term stability and long-term health outcomes.

Patient Education

Optimal management of hypercalcemia requires a blend of evidence-based therapeutics and a disciplined diagnostic strategy that is both cost-conscious and centered on patient preferences. Education should emphasize behaviors that prevent further elevation of calcium while definitive evaluation is underway. Patients benefit from practical guidance on hydration (eg, maintaining steady daily fluid intake unless medically contraindicated) and from tailored dietary counseling that clarifies appropriate use of calcium- and vitamin D–containing products, including over-the-counter supplements and antacids. Medication reconciliation is essential; patients should understand which prescribed or nonprescribed agents may exacerbate hypercalcemia and when to alert clinicians before starting new therapies. For individuals at risk of immobilization-related hypercalcemia, encouraging safe mobilization and physical activity is important. Teaching early warning signs—worsening fatigue, confusion, constipation, polyuria/polydipsia, or palpitations—empowers patients to seek timely care. Effective patient education is most impactful when delivered through interdisciplinary coordination. Primary care clinicians, endocrinologists, nephrologists, oncologists, nurses, pharmacists, and dietitians should align on an accessible plan that clearly explains diagnostic steps (and their rationale), options for acute and longer-term treatment, potential adverse effects, and the patient’s role in self-monitoring. Transparent, two-way communication supports shared decision-making and preserves patient autonomy.

Other Issues

Beyond acute correction of calcium, structured follow-up is critical for durable control and for preventing complications. Patients should be counseled on why serial laboratory monitoring is necessary and how poorly controlled hypercalcemia can affect the heart, kidneys, bones, and cognition. Simple measures—particularly adequate hydration—can meaningfully blunt recurrent rises in calcium and should be reinforced at each visit. A central clinical “pearl” is that treatment choices hinge on the underlying cause. Because therapeutic pathways differ substantially across etiologies (eg, medication-induced hypercalcemia versus primary hyperparathyroidism versus malignancy-related disease), clinicians must pair a careful history and examination with targeted testing to avoid both undertreatment and unnecessary interventions. Another frequent pitfall is missing persistent mild hypercalcemia in minimally symptomatic patients; even modest, sustained elevations warrant evaluation to exclude clinically significant disease and to mitigate cumulative end-organ effects. Educating patients about the importance of ongoing assessment—even when they feel well—improves safety and outcomes.

Enhancing Healthcare Team Outcomes

Hypercalcemia is often first identified either incidentally on routine laboratory panels or during assessment of nonspecific symptoms. Early recognition and coordinated management reduce morbidity and, in high-risk etiologies, may improve survival. Care is inherently multidisciplinary. Primary care and family physicians commonly detect the abnormality and initiate the initial workup and stabilization. Endocrinologists refine the differential diagnosis, oversee parathyroid-related disorders, and guide long-term strategies; nephrologists are pivotal when renal impairment complicates management or when dialysis is contemplated for severe, refractory cases. Oncologists coordinate evaluation and treatment when malignancy is suspected or confirmed. Pharmacists play a key role in identifying drug-induced hypercalcemia, recommending safer alternatives, counseling on supplement interactions, and assisting with monitoring plans. In hospital settings, nurses and ancillary staff expedite laboratory testing, administer hydration and calcium-lowering therapies, monitor for arrhythmias or medication adverse effects, and reinforce education at the bedside. In outpatient environments, additional team members may manage infusions, track prior authorizations, and ensure continuity between specialty visits. Patients and families are essential partners in care. Their participation—tracking symptoms, adhering to medication and hydration plans, and attending follow-up testing—directly influences outcomes. For hypercalcemia associated with immobilization, collaboration with physical and occupational therapy supports graded activity, mobility aids, and hydration strategies, thereby addressing a modifiable driver of calcium excess. When hypercalcemia accompanies advanced malignancy, the clinical trajectory can be guarded; early integration of palliative care supports symptom control, goal-concordant decision-making, and smooth transitions to hospice when appropriate. In sum, educating patients, prioritizing etiology-driven diagnosis, and orchestrating a coordinated, interprofessional response are the cornerstones of high-quality hypercalcemia care. This approach enhances safety, aligns treatments with patient goals, and sustains improvements beyond the acute episode.

Conclusion:

Hypercalcemia remains a multifaceted metabolic disturbance in which timely recognition, rigorous etiologic classification, and judicious therapy determine outcomes. This review underscores three pillars of effective practice. First, anchor evaluation to the parathyroid hormone (PTH) branch point and stratify severity, because the distinction between PTH-mediated and PTH-independent disease drives diagnostic yield and therapeutic selection. Second, pair stabilization with durable control: restore intravascular volume and correct electrolytes, use calcitonin for rapid but transient lowering, and institute antiresorptives—preferably zoledronic acid or denosumab—for sustained effect. Third, treat the cause: resect hyperfunctioning parathyroid tissue when criteria are met, withdraw or substitute offending drugs, mobilize when immobilization is contributory, deploy glucocorticoids in calcitriol-mediated states, and use dialysis for life-threatening or refractory hypercalcemia. Spurious elevation from hemoconcentration should be excluded by reassessing calcium after rehydration. Persistently mild, "asymptomatic" hypercalcemia warrants workup to prevent cumulative skeletal and renal injury. Testing should be hypothesis-driven; excessive, low-yield panels delay care and inflate costs. Age-appropriate cancer screening and focused imaging accelerate diagnosis of malignancy-related hypercalcemia, where prognosis is guarded and early palliative engagement may be appropriate. Longitudinal follow-up monitors bone density, renal function, recurrence, and treatment toxicity. Finally, outcomes improve when patients are active partners. Education about hydration, prudent use of calcium and vitamin D products, recognition of red-flag symptoms, and the purpose of surveillance fosters adherence and shared decision-making. Coordinated, interprofessional care—linking primary care, endocrinology, nephrology, oncology, nursing, pharmacy, rehabilitation, and palliative services—delivers safe, goal-concordant management. An etiology-driven, severity-informed strategy is therefore the cornerstone of modern, patient-centered care for hypercalcemia.

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