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Hypercalcemic Crisis: A Clinical Review

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ABSTRACT

Hypercalcemia is a common metabolic perturbation. However, hypercalcemic crisis is an unusual endocrine emergency, with little clinical scientific data to support therapeutic strategy. We review the relevant scientific English literature on the topic and review current management strategies after conducting a PubMed, MEDLINE, and Google Scholar search for articles published between 1930 and June 2014 using specific keywords: "hypercalcemic crisis," "hyperparathyroid crisis," "parathyroid storm," "severe primary hyperparathyroidism," "acute hyperparathyroidism," and "severe hypercalcemia" for articles pertaining to the diagnosis, epidemiology, clinical presentation, and treatment strategies. Despite extensive clinical experience, large and well-designed clinical studies to direct appropriate clinical care are lacking. Nonetheless, morbidity and mortality rates have substantially decreased since early series reported almost universal fatality. Improved outcomes can be attributed to modern diagnostic capabilities, leading to earlier diagnosis, along with the recognition that primary hyperparathyroidism is the most common etiology for hypercalcemic crisis. Hypercalcemic crisis is an unusual endocrine emergency that portends excellent outcomes if rapid diagnosis, medical treatment, and definitive surgical treatment are expedited.

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KEYWORDS: Crisis; Emergency; Hypercalcemia; Parathyroid crisis

Hypercalcemic crisis is an unusual complication of hypercalcemia that is encountered with decreasing frequency in modern clinical practice. The most common presentation involves a patient with long-standing mild, asymptomatic hypercalcemia resulting from benign primary hyperparathyroidism, presenting with acute decompensation and "new" marked hypercalcemia. Fortunately, timely recognition, diagnosis, and intervention result in excellent outcomes.[1]

DEFINITIONS AND EPIDEMIOLOGY

Hypercalcemic crisis has no uniform standard definition, which makes direct comparison among different studies in the literature difficult. However, a reasonable, yet arbitrary definition may be: an albumin-corrected serum calcium level >14 mg/dL; associated with the presence of multiorgan dysfunction. Typically, organ dysfunction is associated with, or a direct result of, hypercalcemia. The diagnosis should also be considered in severely symptomatic patients despite less marked hypercalcemia.

By 2007 there had been fewer than 350 individual patients with hypercalcemic crisis reported in the literature. However, this is likely to be under-reported, reflecting the heterogeneity of definitions, etiologies, and symptoms attributable to hypercalcemia.[2,3]

Primary hyperparathyroidism is the most common underlying etiology.[1] Parathyroid crisis, parathyroid storm, hyperparathyroid crisis, parathyroid intoxication, parathyroid poisoning, and acute hyperparathyroidism are terms used interchangeably to denote crisis from primary hyperparathyroidism. A large series between 1978 and 2007 reported 252 subjects with crisis attributable to primary hyperparathyroidism.[2] The majority were female (65%), in contrast with other reports indicating a slightly higher incidence in men.[3-7] All age groups are affected, with no specific age predominance. Four percent of women presented during pregnancy.[2] Of the 252 subjects in this series,

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192 had surgical pathology reported. A single parathyroid adenoma was present in 88%. Eight percent of adenomas were located ectopically; including the mediastinum, thymus, tracheoesophageal groove, and retrosternal regions. The mortality rate in this series was 7%. Early series mortality rates approached 100% in patients without timely surgical resection.[3]

Primary hyperparathyroidism is the most common cause of hypercalcemia in ambulatory patients and is often incidentally diagnosed on routine laboratory testing. Single, benign parathyroid adenomas constitute 80%-85% of cases. Diffuse parathyroid gland hyperplasia, double adenomas, and parathyroid carcinoma are far less common. Hanes, in 1938, was the first to report a case of hypercalcemic crisis resulting from parathyroid adenoma.[8] **Table 1** lists potential etiologies of hypercalcemia.

Hypercalcemic crisis is a rare entity in modern practice. A surgical series of patients with primary hyperparathyroidism from the 1970s included 882 subjects and reported only 1.6% presenting in crisis. A more recent single-center series of 1310 consecutive hyperparathyroid patients who underwent parathyroidectomy over a 40-year period reported a 6.7% incidence of crisis.[4]

CLINICAL SIGNIFICANCE

- Despite extensive clinical experience and large case series, prospective studies on Hypercalcemia crisis, which could direct evidence-based clinical care, are lacking.
- Hypercalcemic crisis remains an unusual endocrine emergency.
- Primary hyperparathyroidism is the most common underlying etiology.
- Despite early reports of near universal mortality, modern management has substantially improved outcomes.

CLINICAL PRESENTATION

Hypercalcemic crisis usually evolves from preexisting modest hypercalcemia into an acute severe hypercalcemic exacerbation. Many patients with primary hyperparathyroidism are asymptomatic. However, subtle nonspecific symptoms are often present and attributed to other conditions, making the distinction between symptomatic and asymptomatic mild hypercalcemia troublesome.

Hypercalcemia impacts most organ systems. Gastrointestinal concerns are common and include anorexia, dyspepsia, constipation, nausea, vomiting, and abdominal pain. Pancreatitis, which may be severe and necrotizing, is more common in patients with crisis.[2,9,10] However, it may be argued that pancreatitis re-classifies an uncomplicated patient as one with severe disease, implying crisis.[6,11-13] In a large single-center series of over 1300 patients who underwent parathyroidectomy for primary hyperparathyroidism, the incidence of pancreatitis, altered sensorium, and fatigue were more common in crisis subjects than those with more modest hypercalcemia.[4] Renal manifestations include dehydration, polydipsia, oliguria, acute kidney injury, and nephrocalcinosis. Renal colic may be the presenting complaint. Neurological features are more subtle and include minor neuromuscular symptoms and muscle weakness. Cognitive disturbances include confusion, poor concentration, and personality changes that range from irritability to lethargy and coma. Cardiovascular manifestations include a shortened QT interval with increased susceptibility to arrhythmias and accelerated vascular calcification.

DIAGNOSTIC AND PATHOLOGICAL CONSIDERATIONS

Diagnostic evaluation should focus on establishing or refuting a diagnosis of primary hyperparathyroidism. Frankly elevated or inappropriately normal serum levels of intact parathormone in the presence of hypercalcemia are indicative of primary hyperparathyroidism. History and physical examination should direct further laboratory investigation. Serum parathyroid hormone-related peptide may be elevated in a patient with known cancer. However, local cytokines, osteolytic factors, or production of 1,25-dihydroxyvitamin D by malignant tumor may be responsible for inducing hypercalcemia in malignancy.

There are many other well-described etiologies of hypercalcemia (**Table 1**). However, most are less likely to lead to severe hypercalcemia. Clinicians should keep a broad differential diagnosis in mind when deciding on the utility of ordering further investigations in the work-up. For example, the incidence of hypercalcemia in sarcoidosis is approximately 10%, although hypercalciuria occurs 3 times more frequently.[14] Hypercalcemic, ill, or immobilized patients may decompensate into crisis following calcium mobilization from the skeleton into the extra-skeletal circulation. This is of potential concern with active bone turnover such as in growing children or patients with Paget's disease. Mild hypercalcemia may be exacerbated by high-dose vitamin D and medications including thiazide diuretics, lithium, or calcium-containing antacids. The milk-alkali syndrome is an infrequent etiology of significant hypercalcemia, except for a few sporadic cases described in pregnancy.

Mildly elevated or inappropriately normal parathormone in the face of severe hypercalcemia should prompt consideration of an additional underlying process other than isolated primary hyperparathyroidism. Primary hyperparathyroidism complicated by sarcoidosis, thyrotoxicosis, and immobilization may result in decompensated crisis.[15]

Preoperative localization of parathyroid adenomata with imaging techniques such as ultrasonography, computed tomography, magnetic resonance imaging, and nuclear medicine scintigraphy are accepted in modern practice. Once the diagnosis of primary hyperparathyroidism is biochemically established, imaging modalities should complement, not

Table 1 Causes of Hypercalcemia

Parathyroid disease
Primary hyperparathyroidism due to benign PTH adenoma, PTH carcinoma, or PTH multiglandular hyperplasia as part of multiple endocrine neoplasia syndromes
Tertiary hyperparathyroidism
Malignancy
Parathyroid hormone related protein (humoral hypercalcemia of malignancy)
Local osteolysis mediated by cytokine release
Lytic bone metastasis.
Multiple myeloma
Ectopic production of 1, 25 dihydroxyvitamin D by the tumor (eg, lymphoma)
Endocrinopathies
Adrenal insufficiency
MEN 1, 2A
Thyrotoxicosis
Pheochromocytoma
VIPoma
Granulomatous disease
Tuberculosis
Sarcoidosis
Endemic mycosis: histoplasmosis, coccidioidomycosis
Leprosy
Crohn's disease
Berylliosis
Medications
Estrogens
Lithium
Thiazide diuretics
Excess vitamin D or vitamin A ingestion
Miscellaneous
Familial hypocalciuric hypercalcemia
Immobilization

MEN = multiple endocrine neoplasia; PTH = parathyroid hormone.

supplant, clinical and biochemical evaluation. Ectopic parathyroid adenoma is more frequently reported in patients with crisis.[16] Common ectopic locations include the tracheoesophageal groove, mediastinum, and thymus. Individuals with biochemically established primary hyperparathyroidism and crisis should have sequential imaging performed until the source is located, bearing in mind increased frequency of ectopic locations. Various imaging modalities have respective strengths and weaknesses.[17] Initial imaging modality choice should be dictated by local expertise and technology availability. An initial approach to preoperative anatomic localization that has high sensitivity and specificity, without ionizing radiation exposure, is thorough neck ultrasound. Ultrasound-guided needle aspiration with analysis of the aspirate for parathormone will confirm an adenoma in the neck. Additional benefits of ultrasound include low cost, safety, short duration, and potential availability in the practitioner's office. Disadvantages include limited visualization of ectopic locations and dependence on operator experience and availability. If ultrasonography is unrevealing, occurring in 10%-20% of cases with experienced ultrasonographers,[18] a nuclear scintigraphy parathyroid scan should be obtained including images of the mediastinum and chest. If both are negative, a 4-dimensional computed tomography scan might be helpful.[19]

Pathological evaluation of resected parathyroid in patients with severe hypercalcemia most often reveals a single chief-cell adenoma. Parathyroid carcinoma and hyperplasia are rare, although electron microscopy studies have reported increases in lysosomal bodies in these cells, reflecting high levels of synthesis and release of hormone.[20] Some surgical series support the construct that primary hyperparathyroidism resulting in crisis occurs in individuals with larger adenomas,[4] which include adenomas with hemorrhagic, degenerative features.[21-23] Parathyroid carcinoma may be more common in crisis than those with modest hypercalcemia. A large retrospective, single-center series of subjects with primary hyperparathyroidism reported a relatively high proportion of patients with crisis and parathyroid carcinoma (4.5%).[24]

MEDICAL AND SURGICAL TREATMENT

Hypercalcemic crisis has the potential for high mortality if not treated promptly.[25] The vast majority of the literature addressing the nonsurgical treatment of severe hypercalcemia pertains to the defined group of hypercalcemia of malignancy, making direct extrapolation to other etiologies somewhat empiric.

Goals of therapy are aimed at: 1) lowering calcium levels, 2) correcting dehydration, and thereby increasing renal calcium excretion, and 3) decreasing osteoclast-mediated bone resorption. Management of the underlying cause of hypercalcemia directs treatment strategy.[2] In the majority of patients, definitive curative therapy requires surgical parathyroidectomy.

The exact timing of parathyroidectomy to ensure optimal outcome is not definitively established, with no good prospective data to guide decisions on surgical timing. Recent case series favor early surgery after a period of medical optimization, rather than emergency surgery. The precise definitions of "early" vs "emergency" surgery are variable. In one study, mean interval between presentation and operative intervention was 8 days, allowing time for work-up and management of concurrent medical problems. Mortality from crisis documented in this "early surgery" series was negligible.[2] While medical optimization preoperatively may seem prudent, a single-center retrospective series including 35 years of data reported no significant differences in long-term survival in patients who underwent surgery within 72 hours, compared with those treated medically for >72 hours before surgery.[24] It may be reasonable to prioritize medical management while work-up and diagnostics are pursued. Surgery should be expedited, taking into consideration patient suitability and comorbidity.

High-quality, prospective clinical trial data addressing nonoperative management of hypercalcemic crisis is

limited. Based on several large series, medical management of crisis is best accomplished through a combination of forced diuresis and bisphosphonate therapy.[2,4,24]

Individuals with crisis are usually hypovolemic and sodium depleted resulting from natriuresis and increased urine output induced by hypercalcemia. Calcium and sodium excretion are intimately related and renal tubular reabsorption of sodium is suppressed by hypercalcemia.[26] Intravenous fluid needs to be adjusted on an individualized basis, depending on both the degree of dehydration and underlying cardiac and other comorbid disease. A practical approach consists of 3 to 4 L of saline infused for 24 hours, followed by 2 to 3 L per 24 hours thereafter until adequate urine output (2 L/day) is established.

Saline infusion reduces hypercalcemia in most patients but will not restore normocalcemia in individuals with severe hypercalcemia.[27-29] Intravenous volume expansion increases glomerular filtration rate, increasing the filtered calcium load through the glomerulus and inhibits calcium re-absorption in the proximal nephron. Sodium promotes calciuresis at the distal nephron, which permits safe use of loop diuretics to further calciuresis, while avoiding the deleterious effects of fluid overload. Generally, a 1.6−2.4-mg/dL reduction in the serum calcium may be expected with isotonic saline infusion.[27,28,30,31]

Loop diuretics are often combined with isotonic saline infusion. They block calcium re-absorption in the ascending limb of the loop of Henle, inducing calciuresis. Diuretic therapy should not be considered before correction of hypovolemia, given the risk of circulatory collapse. If high doses are routinely prescribed, this may limit the clinical utility leading to adverse effects.[32] Aggressive renal sodium and extracellular volume loss may exacerbate tenuous renal function. Individuals with limited cardiac reserve and those unable to tolerate large volumes of intravenous saline would be ideal candidates to promote the calciuretic effect of saline, while allowing room for expansion of intravascular volume. Thiazide diuretics are contraindicated in severe hypercalcemia. They enhance calcium re-absorption in the distal nephron and may exacerbate hypercalcemia.

Bisphosphonate therapy is highly effective in lowering calcium levels in hypercalcemia of malignancy. However, their efficacy and safety in hypercalcemia resulting from other causes is less clear. They are not approved by the Food and Drug Administration in the US for use in non-cancer hypercalcemia. They work by blocking osteoclast-mediated bone resorption via promotion of osteoclast apoptosis. Oral bisphosphonate bioavailability is limited, and nausea, anorexia, and vomiting are frequent concerns in patients with severe hypercalcemia. As a result, intravenous bisphosphonates are preferred. Bisphosphonates currently approved by the Food and Drug Administration for treatment of hypercalcemia of malignancy are pamidronate and zoledronate. They are superior to other modes of treatment, including volume repletion, loop diuretics, and the combination of glucocorticoids and calcitonin.[33] Unless contraindicated, they should be regarded as first-line therapy, in conjunction with intravenous volume expansion.

Etidronate, the first bisphosphonate used for treatment of hypercalcemia, had a modest effect, with calcium lowering in the range of 15%-40%.[34] It is no longer marketed or approved for this indication in the US and has been replaced by the more potent pamidronate.[35,36] In hypercalcemia secondary to primary hyperparathyroidism, limited data on pamidronate use is available. In one report of 9 patients with moderate to severe hypercalcemia, a single dose of 15-60 mg resulted in therapeutic response in 8 of 9 patients.[36] The recommended dose is 30 mg for mild, and 60-90 mg for severe, hypercalcemia. Calcium levels start to fall within 2 days of administration, with a nadir reached around day 6. Overall duration of action is reported to be 28-30 days.[36,37]

Zoledronate is a highly active and potent intravenous bisphosphonate approved for treatment of hypercalcemia of malignancy in the US in 2001. It has the advantage of rapid infusion over 5-15 minutes, compared with the recommended 2-hour infusion time for pamidronate. In head-to-head trials it has been reported to be superior to pamidronate in restoring normocalcemia in hypercalcemia of malignancy (86%-88% for zoledronate vs 70% for pamidronate).[38] In addition, calcium reductions may occur slightly sooner after zoledronate infusion. The current recommended doses are 4 mg intravenously for initial treatment and 8 mg for relapse. The 2007 American Society of Clinical Oncology guidelines recommended that full doses of pamidronate be given over at least 2 hours and zoledronate be infused over 15 minutes in patients with normal kidney function. In those with reduced creatinine clearance between 30 and 60 mL/min, the zoledronate dose should be reduced, but no change in the dose of pamidronate is recommended. In patients with creatinine clearance <30 mL/min, zoledronate is not recommended and pamidronate infusion time should be extended to 4-6 hours, along with consideration given to dose reduction. Ideally, serum creatinine levels should be obtained before each dose and the next dose should be withheld in patients with a significant increase from baseline.[39,40]

Several other agents commonly used before the advent of bisphosphonates are now rarely indicated, with less efficacy and increased adverse events. Drugs such as mithramycin, intravenous phosphate, and gallium nitrate are of largely historical interest, but may be considered if bisphosphonates are ineffective or contraindicated. **Table 2** lists typical modalities useful for treatment of hypercalcemic crisis.[27,28,30,37,38,41-46]

Calcitonin is a safe, valuable agent that should be considered in the treatment of hypercalcemic crisis. It has the most rapid onset of action of all available drugs and has been used successfully in combination with intravenous bisphosphonates in patients with severe hypercalcemia. Combination therapy results in more rapid reductions in calcium levels than obtained with bisphosphonates alone.[47,48] Calcitonin lowers calcium levels by reducing osteoclastic bone resorption and promoting calciuresis. The

Table 2 Modalities for Use in the Treatment of Hypercalcemic Crisis

Intervention	Drugs	Specific Indication	Dose	Mechanism of Action	Adverse Effects
Volume repletion[27,28]	0.9% NS	Dehydration	2 to 4 liters per day, with goal urine output >2 L/day	Increases filtration of calcium by increasing GFR, decreases proximal tubular reabsorption and promotes calciuria in kidneys	Fluid overload, CHF exacerbation in patients with compromised cardiac or renal function
Diuresis[27,30,41,42]	Loop diuretics like furosemide	Fluid overload	40 mg to 80 mg up to 500 mg/day	Blocks calcium reabsorption in loop of Henle	Dehydration, electrolyte abnormalities like hypokalemia
Intravenous Bisphosphonate	Pamidronate[37,43,44]	HC in addition to IVF and diuresis	60 mg to 90 mg IV over a period of 2 hours	Inhibits FPPS enzyme of mevalonate pathway in osteoclast.	Severe musculoskeletal pain, renal failure
	Zoledronate[38]	As above	4 mg to 8 mg IV over a period of 15 minutes	As above	As above, flu-like syndrome, and atrial fibrillation
Dialysis[45,46]	Hemodialysis or peritoneal dialysis	HC with renal failure, heart failure when above treatment modalities are contraindicated	Calcium free dialysate	Removes calcium from circulation	Dialysis-related complications like hypovolemia, hypotension

CHF = congestive heart failure; GFR = glomerular filtration rate; FPPS = farnesyl pyrophosphate synthase; HC = hypercalcemic crisis; IV = intravenous; IVF = intravenous fluids; NS = normal saline.

rapid onset, within 12-24 hours, with modest effect, is thought to be due to the calciuretic effect, with approximately 1 mg per deciliter reductions in calcium levels.[44] Calcitonin monotherapy lacks both potency and durability. The transient effect results from downregulation of calcitonin receptors in target cells in bone and the kidney and the development of tachyphylaxis within 48 hours.[49] However, where rapid calcium lowering is desirable, it is highly valuable as a temporizing agent to facilitate reductions while waiting for more potent, slower-acting bisphosphonates to become effective. Combination calcitonin and bisphosphonates, in addition to forced diuresis, may therefore be most valuable in acutely ill patients where rapid calcium lowering is warranted.[29,47,48]

Glucocorticoids are useful in a limited subset of individuals. Multiple myeloma and lymphoma-related hypercalcemia respond, in part, due to the antineoplastic effect of suppressing growth of lymphoid neoplasia. However, unless the tumor responsible for hypercalcemia is inherently corticosteroid responsive, these agents are ineffective. Additionally, hypercalcemia resulting from elevated levels of 1,25 dihydroxyvitamin D seen in granulomatous disease and hypervitaminosis D is due to dysregulated production of 1,25 dihydroxyvitamin D from precursor 25 hydroxyvitamin D3 through 1-alpha hydroxylase CYP27B1 in activated macrophages. Glucocorticoids inhibit this process. Glucocorticoids also lower calcium by several other mechanisms, including reduced calcium resorption from bone and intestinal absorption, as well as having a modest impact on increasing renal calcium excretion. Doses of prednisone in the range of 1-2 mg/kg, or hydrocortisone 200-300 mg daily for 3 to 5 days may be considered.[50-52]

Dialysis against a low calcium dialysate is valuable in patients with renal impairment, or as salvage therapy where other options have failed or are contraindicated.[50] There are no specific evidence-based data to guide clinicians as to which individuals are most likely to benefit.

Medical treatment of primary hyperparathyroidism with crisis should be regarded as a temporary measure aimed to "bridge" individuals towards parathyroidectomy.[2] Postoperatively, patients with crisis may develop symptomatic hypocalcemia with potential tetany if hypocalcemia is not anticipated. Parathormone levels normalize rapidly following parathyroidectomy, whereas calcium levels improve over several days. Resolution of the complex metabolic changes resulting from hypercalcemia may take up to 6-12 months, and many of the skeletal manifestations improve only slightly.[3,53]

Novel options for the treatment of severe hypercalcemia are in development. Recent studies have reported therapeutic benefit in hypercalcemic crisis with infliximab in Crohn's disease and sarcoidosis.[54,55]

Parathyroid carcinoma rarely leads to crisis, but a potential treatment for this condition may be the calcimimetic

agent, cinacalcet, which has shown some benefit in moderating calcium elevation.[56]

CONCLUSION

Hypercalcemic crisis is a rare manifestation of decompensated calcium homeostasis, most often resulting from primary hyperparathyroidism. Timely work-up and intensive medical therapy to optimize organ function should be prioritized, while urgent surgery by an experienced endocrine surgeon is expedited. Aggressive saline volume expansion and bisphosphonates are first-line therapy and should be instituted as a bridging measure as surgery is expedited. Long-term outcomes with combined medical and surgical management are excellent.

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