

Hypocalcemia in acute pancreatitis revisited

Armin Ahmed, Afzal Azim, Mohan Gurjar, Arvind Kumar Baronia

Abstract

Hypocalcemia is a frequent finding in acute pancreatitis. Severe hypocalcemia can present with neurological as well as cardiovascular manifestations. Correction of hypocalcemia by parenteral calcium infusion remains a controversial topic as intracellular calcium overload is the central mechanism of acinar cell injury in pancreatitis. The current article deals with the art and science of calcium correction in pancreatitis patients.

Keywords: Acute pancreatitis, calcium, hypocalcemia

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The Scenario

A 30-year-old orthopedic surgeon developed severe pain in abdomen while going for morning rounds. Investigations showed serum amylase of 750 U/L and serum lipase of 860 U/L. Ultrasound of the abdomen was suggestive of acute pancreatitis with multiple gall stones. Contrast-enhanced computed tomography (CT) of the abdomen showed a CT severity index of 7. On day 4 of pancreatitis, the patient was intubated and started on mechanical ventilation on account of worsening tachypnea. Noradrenaline and vasopressin infusions were started to maintain a target mean arterial pressure of 65 mmHg. His other investigations were as following; hemoglobin 9 g%, white blood cell count 25,000/cumm, serum albumin 3.5 g/dl, Na⁺ 135 mEq/L, K⁺ 4 mEq/L, ionized calcium (iCa⁺⁺) 0.7 mmol/L, and Mg⁺⁺ 2 mg/dl. The doctor's resident on duty started him on intravenous calcium infusion. On questioning, he said that a patient on high sedation may not show signs of neuromuscular irritability. Has he done the right intervention?

Introduction

Hypocalcemia is commonly found in patients requiring

intensive care, more so in patients with severe acute pancreatitis. Frequently physicians tend to correct electrolyte abnormalities found in critically ill patients as these deviations are considered harmful. Beneficial effects of maintaining normal potassium and magnesium level is well supported by literature but the same is not true for calcium.^[1]

Literature Search

A literature search on PubMed and EMBASE was done using search terminologies such as "hypocalcemia in pancreatitis," "hypocalcemia correction," and "parenteral calcium infusion." We also manually searched the references of relevant articles.

Calcium Homeostasis

Normal range of serum calcium is 8.5–10.5 mg/dl (2.1–2.6 mmol/L). Serum calcium exists as nonionized (bound to albumin) and ionized form (physiologically

From:

Department of Critical Care Medicine, SGPGIMS, Lucknow, Uttar Pradesh, India

Correspondence:

Dr. Armin Ahmed, Department of Critical Care Medicine, SGPGIMS, Raebareli Road, Lucknow, Uttar Pradesh, India.
E-mail: drarminahmed@gmail.com

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active). Some of the nonionized forms are also bound to anions such as citrate, bicarbonate, and phosphate. Calculation of the “corrected calcium” from measured calcium level by the help of various algorithms and formulae is no more considered a good surrogate.^[2] Direct measurement of iCa makes more sense as it is the ionized form, which is physiologically active. Normal serum level of calcium is maintained by the action of parathyroid hormone (PTH). PTH maintains serum calcium level by causing calcium re-absorption from kidneys and bones and Vitamin D-mediated calcium absorption by gastrointestinal tract. Magnesium is required for secretion as well as action of PTH; therefore, hypomagnesaemia causes hypocalcemia refractory to correction unless magnesium is normalized. Hypocalcemia is defined as $iCa < 1.12$ mmol/L. There is discrepancy in the cutoff for severe hypocalcemia. Some authors take value < 0.9 mmol/L as severe whereas others use < 0.8 mmol/L as the cutoff.

Myocytes and neuronal cells are sensitive to serum calcium fluctuations; therefore, clinical features of hypocalcemia are mainly neurological and cardiovascular. These include neuromuscular irritability in the form of perioral numbness, paresthesia, cramps, etc. In severe cases, patients may develop dyspnea or stridor due to the involvement of respiratory muscles, carpopedal spasm (Trousseau’s sign), and facial muscle hyperreflexia (Chvostek sign). Other CNS manifestations can be seizures, hallucinations, confusion, etc.^[3] Cardiovascular manifestations include QT prolongation, bradycardia, decreased vascular tone, and hypotension.^[4] Hypocalcemia affects mainly ST segment of electrocardiogram (ECG), leading to increase in QT interval. QT prolongation is directly proportional to the degree of hypocalcemia.^[5]

Hypocalcemia has been correlated with reduced myocardial contractility, and hypocalcemia-induced dilated cardiomyopathy is a well-known entity in literature.^[6,7] Severe hypocalcemia as seen in some of the patients of SAP may theoretically aggravate shock by decreasing cardiac contractility. QT prolongation due to hypocalcemia can precipitate torsade de pointes in patients at risk.

Calcium and Pancreatitis

Calcium plays a central role in the pathogenesis of pancreatitis and our understanding in this field is still evolving. Calcium is required for normal secretory function of the pancreatic acinar cells, but these signals are transient and mainly confined to apical pole. It has been shown that sustained global increase in cytosolic Ca^{++} is responsible for premature trypsinogen activation,

vacuolization, and acinar cell death. Mechanisms involved in maintaining sustained elevated cytosolic calcium in response to stimulus (bile acids/ethanol) are pathological Ca^{++} release from endoplasmic reticulum stores, increased entry of extracellular calcium, and defects in calcium extrusion and re-uptake mechanisms^[8] [Figure 1].

Recent insight into calcium-mediated acinar cell injury suggests that hypocalcemia of SAP might play a protective role by depleting the acinar cells of extracellular supply of calcium.

Hypocalcemia and Pancreatitis

Hypocalcemia is one of the components of Ranson’s scoring system done to assess the severity of pancreatitis. Various studies on animal models have shown that hypocalcemia is a poor prognostic marker in patients with pancreatitis.^[9] Ammori *et al.* reported that hypocalcemia was more frequent during severe attack as compared to mild attack of pancreatitis (86% vs. 39%, $P < 0.001$).^[10] Prevalence of hypocalcemia ranges between 15% and 88% in critically ill patients depending on the setting and cutoffs used.^[11,12]

Exact mechanism of hypocalcemia in acute pancreatitis is unknown. Mechanism of hypocalcemia during early stage (within 1st week) is different from hypocalcemia developing in late phase of the disease. Several mechanisms proposed for hypocalcemia seen in early phase are autodigestion of mesenteric fat by pancreatic enzymes and release of free fatty acids, which form calcium salts, transient hypoparathyroidism, and hypomagnesaemia.^[13-15]

Later stages of pancreatitis are frequently complicated by sepsis, which becomes an important contributor to

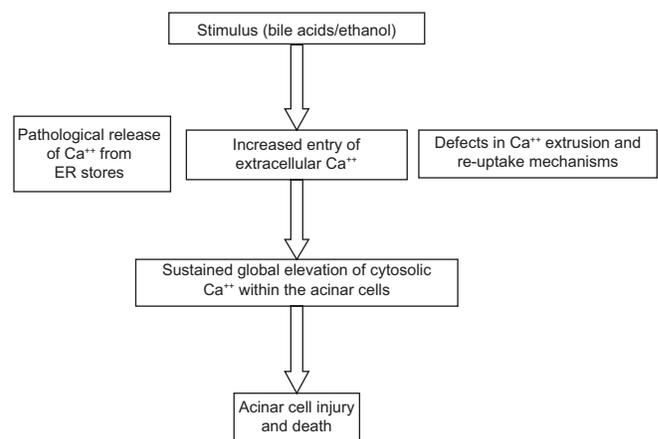


Figure 1: Mechanism of acinar cell injury during pancreatitis endoplasmic reticulum

hypocalcemia. Mechanism of hypocalcemia in sepsis is not clear. Whitted *et al.* proposed that increased circulating catecholamines in sepsis cause a shift of circulating calcium into the intracellular compartment leading to relative hypocalcemia. This causes increased PTH secretion by negative feedback loop leading to further increase in intracellular calcium overload, oxidative stress, and cell death.^[16] Hypomagnesaemia-induced impaired PTH secretion and action, relative PTH deficiency, and Vitamin D deficiency, etc., are some of the other plausible causes.

Hypocalcemia and Mortality

Although we could not find any study dealing specifically with hypocalcemia and its association with mortality in SAP, a few studies have shown that severe hypocalcemia is associated with increased mortality and hospital stay in critically ill patients. The largest multicenter study done was conducted in four hospitals of Australia on a cohort of 7024 patients. The study showed that $iCa < 0.8$ mmol/L was an independent predictor of mortality in Intensive Care Unit (ICU) patients.^[17]

Steele *et al.* in a retrospective single-center observational study on 1038 critically ill patients found that 55.2% patients had hypocalcemia ($iCa < 1.1$ mmol/L) at admission. Serum calcium normalized by day 4 in most patients. Calcium level normalization was not different in patients who received and who did not receive calcium supplementation. Patients with severe hypocalcemia (0.9 mmol/L) who failed to normalize their calcium level by day 4 had increased mortality (38% vs. 19%); however, the values did not reach statistical significance. Authors suggested that hypocalcemic patients who fail to correct their level spontaneously might form the subgroup of patients likely to benefit from intervention.^[18]

Parenteral Calcium Infusion

Literature regarding hypocalcemia in pancreatitis is scarce. To the best of our knowledge, there is no study on the effect of hypocalcemia correction in pancreatitis patients.

Studies in other subgroup of population suggest detrimental role of parenteral calcium infusion. In a study on 217 living donor liver transplant patients, Chung *et al.* showed that the risk of biochemical acute pancreatitis (BAP) after transplant was increased in proportion to the amount of intravenous calcium chloride administered during preanhepatic phase and serum calcium surge during initial 2 h after liver graft reperfusion. Authors

suggested that sustained hypercalcemia could not be the mechanism behind BAP in these patients because none of the serum calcium exceeded upper limit during whole liver transplant surgery. Acute challenge with large amount of calcium may cause sudden rise in serum calcium level and pancreatic acinar damage. The risk of BAP increased abruptly at >1250 mg (>450 mg/h) calcium administration.^[19]

Collage *et al.* studied calcium level in 526 septic ICU patients, out of which 377 (71.7%) had hypocalcemia and 93 (17.7%) had received calcium supplementation. Mortality was not higher in hypocalcemia patients, but administration of intravenous calcium was associated with an increased risk of death and worsening of organ failure. Patients who received calcium supplementation had significantly higher APACHE III scores. They also showed in a murine model that calcium/calmodulin-dependent protein kinases were involved in worsening of organ failure by exaggerated inflammatory response with calcium administration.^[20]

Despite the frequent presence of hypocalcemia in critically ill patients, correction of iCa has not been shown to improve hemodynamic profile in animal models of sepsis.^[21,22] It has been postulated that hypocalcemia is a bystander and marker of severity of illness and does not play causative role, therefore correction of hypocalcemia is unwarranted in critically ill patients [Table 1].

Patients who are on mechanical ventilation may not show early features of neuromuscular irritability due to sedation and paralysis. In such a situation, the approach should be individualized and a close watch should be kept on QTc interval.

In the above described case, the resident doctor should have monitored the QTc interval and corrected calcium only if it was prolonged more than 0.44 s. Each 10 ml ampoule of calcium chloride and calcium gluconate contains 272 mg and 90 mg elemental calcium, respectively [Table 2]. Rise in serum calcium level after a bolus dose is transient and levels begin to fall after 30 min. Therefore, a bolus dose should be followed by infusion of 0.5–1.5 mg of elemental calcium/kg/h until symptoms recover.^[26] Response to calcium infusion may vary from patient to patient. Therefore, therapy should be optimized by regular monitoring of iCa level and subsequent dose titration. Continuous ECG monitoring is needed during intravenous calcium infusion.

Calcium infusion can lead to skin necrosis. Parenteral administration should be done only via a central venous

Table 1: Calcium administration in severe hypocalcemia

Argument	Studies	Principle findings
Pros		
Hypocalcemia is associated with increased mortality	Miura <i>et al.</i> ^[23] Egi <i>et al.</i> ^[17] Steele <i>et al.</i> ^[18]	Hypocalcemia is an independent predictor of all-cause mortality in patients with heart failure and chronic kidney disease Severe hypocalcemia (<0.8 mmol/L) is an independent predictor of mortality in critically ill patients Severe hypocalcemia patients who fail to normalize their calcium level by day 4 of ICU stay show increased mortality as compared with those who normalize
Calcium administration can increase myocardial contractility and vascular tone	Vincent <i>et al.</i> ^[24]	In a pilot study of 17 critically ill patients with hypocalcemia, correction of calcium levels resulted in a significant increase in arterial pressure lasting at least an hour
Though rare hypocalcemia-induced dilated cardiomyopathy is a well-known entity in literature	Benzarouel <i>et al.</i> ^[6]	Case report of two cases of hypocalcemia-induced dilated cardiomyopathy which improved after calcium correction
Cons		
Calcium plays a central role in the pathogenesis of pancreatitis	Mithöfer <i>et al.</i> ^[25] Chung <i>et al.</i> ^[19]	Acute experimental hypercalcemia induced in rat model resulted in dose-dependent changes characteristic of acute pancreatitis Risk of BAP increased in proportion to the amount of intravenous calcium chloride given during preanhepatic phase and serum calcium surge during initial 2 h after liver graft reperfusion in living donor liver transplant patients
In spite of frequent occurrence of hypocalcemia in critically ill patients, calcium correction has not been shown to be beneficial in animal studies	Carlstedt <i>et al.</i> ^[21] Steinhorn <i>et al.</i> ^[22]	In porcine model of endotoxemia, calcium administration did not significantly lead to improvement in hemodynamics or survival Calcium supplementation did not cause any additional benefit in experimental model of acute sepsis in dogs
Calcium supplementation has been found to be associated with increased mortality in animal models	Collage <i>et al.</i> ^[20]	Calcium chloride administrations to septic mice lead to exaggerated inflammation, vascular leak, organ dysfunction, and increased odds of death

BAP: Biochemical acute pancreatitis; ICU: Intensive Care Unit

Table 2: Management protocol for intravenous calcium replacement

Calcium solutions for intravenous use
10 ml of CaCl ₂ =272 mg of elemental calcium
10 ml of calcium gluconate=90 mg of elemental calcium
In symptomatic patients (QTc prolongation, carpopedal spasm, seizures, etc.)
Bolus; 1-2 mg elemental calcium/kg over 10 min
Infusion; 0.5-1.5 mg elemental calcium/kg/h in adults
1-3 mg elemental calcium/kg/h in children

catheter. Calcium should not be given to patients with hyperphosphatemia as it causes precipitation and deposition of calcium phosphate salts in various tissues. Hyperphosphatemia correction should be done before intravenous calcium supplementation, maintaining calcium-phosphate product below 4.4 mmol²/L² (55 mg²/dl²).

Hypercalcemia-Induced Pancreatitis

Hypercalcemia is one of the causes of acute pancreatitis. Frick *et al.* in a study on rat model reported that hypercalcemia induces pancreatitis by causing secretory block and accumulation of secretory proteins.^[27] Bai *et al.* reviewed 10 studies dealing with primary hyperparathyroidism (PHPT).^[28] Except for two studies, rest all showed an increased rate of pancreatitis in patients of PHPT. Hypercalcemia has been implicated as the cause of pancreatitis in PHPT patients. Pooled data showed resolution of pancreatitis attacks in 49% PHPT patients after parathyroidectomy. It has been postulated

that high extracellular calcium leads to increased cellular calcium-mediated calcineurin activation and pathological activation of pancreatic proteases.

Rarely, patients of multiple myeloma can present with hypercalcemia-induced pancreatitis.^[29]

Conclusion

Hypocalcemia correction should be done with extreme caution in patients of acute pancreatitis as calcium plays a central role in the pathogenesis of acinar injury and cell death. There is no evidence to support calcium correction by parenteral calcium infusion in patients with mild to moderate hypocalcemia (iCa 0.9-1 mmol/L). Literature is scarce regarding the role of parenteral calcium in severe hypocalcemia. Approach toward severe hypocalcemia should be individualized depending on other risk factors and frequency of monitoring. Magnesium is required for secretion as well as action of PTH. Hypomagnesaemia is a common finding in alcoholics, malnourished patients, and patients on diuretic support. Therefore, magnesium correction should be instituted before the correction of hypocalcemia.

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Conflicts of interest

There are no conflicts of interest.

References

- Forsythe RM, Wessel CB, Billiar TR, Angus DC, Rosengart MR. Parenteral calcium for intensive care unit patients. *Cochrane Database Syst Rev* 2008;4:006163.
- Slomp J, van der Voort PH, Gerritsen RT, Berk JA, Bakker AJ. Albumin-adjusted calcium is not suitable for diagnosis of hyper- and hypocalcemia in the critically ill. *Crit Care Med* 2003;31:1389-93.
- Riggs JE. Neurologic manifestations of electrolyte disturbances. *Neurol Clin* 2002;20:227-39.
- Fong J, Khan A. Hypocalcemia: Updates in diagnosis and management for primary care. *Can Fam Physician* 2012;58:158-62.
- Gardner JD, Calkins JB Jr., Garrison GE. ECG diagnosis: The effect of ionized serum calcium levels on electrocardiogram. *Perm J* 2014;18:e119-20.
- Benzarouel D, Hasni K, Ashab H, El Hattatou M. A reversible cause of dilated cardiomyopathy: Hypocalcemia. *Ann Cardiol Angeiol (Paris)* 2014;63:102-6.
- Jankowski S, Vincent JL. Calcium administration for cardiovascular support in critically ill patients: When is it indicated? *J Intensive Care Med* 1995;10:91-100.
- Li J, Zhou R, Zhang J, Li ZF. Calcium signaling of pancreatic acinar cells in the pathogenesis of pancreatitis. *World J Gastroenterol* 2014;20:16146-52.
- Dias C, Carreira LM. Serum ionized calcium as a prognostic risk factor in the clinical course of pancreatitis in cats. *J Feline Med Surg* 2015;17:984-90.
- Ammori BJ, Barclay GR, Larvin M, McMahon MJ. Hypocalcemia in patients with acute pancreatitis: A putative role for systemic endotoxin exposure. *Pancreas* 2003;26:213-7.
- Zaloga GP. Hypocalcemia in critically ill patients. *Crit Care Med* 1992;20:251-62.
- Zivin JR, Gooley T, Zager RA, Ryan MJ. Hypocalcemia: A pervasive metabolic abnormality in the critically ill. *Am J Kidney Dis* 2001;37:689-98.
- Condon JR, Ives D, Knight MJ, Day J. The aetiology of hypocalcaemia in acute pancreatitis. *Br J Surg* 1975;62:115-8.
- McMahon MJ, Woodhead JS, Hayward RD. The nature of hypocalcaemia in acute pancreatitis. *Br J Surg* 1978;65:216-8.
- Ryzen E, Rude RK. Low intracellular magnesium in patients with acute pancreatitis and hypocalcemia. *West J Med* 1990;152:145-8.
- Whitted AD, Stanifer JW, Dube P, Borkowski BJ, Yusuf J, Komolafe BO, *et al.* A dyshomeostasis of electrolytes and trace elements in acute stressor states: Impact on the heart. *Am J Med Sci* 2010;340:48-53.
- Egi M, Kim I, Nichol A, Stachowski E, French CJ, Hart GK, *et al.* Ionized calcium concentration and outcome in critical illness. *Crit Care Med* 2011;39:314-21.
- Steele T, Kolamunnage-Dona R, Downey C, Toh CH, Welters I. Assessment and clinical course of hypocalcemia in critical illness. *Crit Care* 2013;17:R106.
- Chung HS, Kim YS, Lee JM, Hong SH, Lee SR, Park CS. Intraoperative calcium-related risk factors for biochemical acute pancreatitis after living-donor liver transplantation. *Transplant Proc* 2011;43:1706-10.
- Collage RD, Howell GM, Zhang X, Stripay JL, Lee JS, Angus DC, *et al.* Calcium supplementation during sepsis exacerbates organ failure and mortality via calcium/calmodulin-dependent protein kinase (CaMKK) signaling. *Crit Care Med* 2013;41:e352-60.
- Carlstedt F, Eriksson M, Kiiski R, Larsson A, Lind L. Hypocalcemia during porcine endotoxemic shock: Effects of calcium administration. *Crit Care Med* 2000;28:2909-14.
- Steinhorn DM, Sweeney MF, Layman LK. Pharmacodynamic response to ionized calcium during acute sepsis. *Crit Care Med* 1990;18:851-7.
- Miura S, Yoshihisa A, Takiguchi M, Shimizu T, Nakamura Y, Yamauchi H, *et al.* Association of hypocalcemia with mortality in hospitalized patients with heart failure and chronic kidney disease. *J Card Fail* 2015;21:621-7.
- Vincent JL, Bredas P, Jankowski S, Kahn RJ. Correction of hypocalcaemia in the critically ill: What is the haemodynamic benefit? *Intensive Care Med* 1995;21:838-41.
- Mithöfer K, Fernández-del Castillo C, Frick TW, Lewandrowski KB, Rattner DW, Warshaw AL. Acute hypercalcemia causes acute pancreatitis and ectopic trypsinogen activation in the rat. *Gastroenterology* 1995;109:239-46.
- Kelly A, Levine MA. Hypocalcemia in the critically ill patient. *J Intensive Care Med* 2013;28:166-77.
- Frick TW, Mithöfer K, Fernández-del Castillo C, Rattner DW, Warshaw AL. Hypercalcemia causes acute pancreatitis by pancreatic secretory block, intracellular zymogen accumulation, and acinar cell injury. *Am J Surg* 1995;169:167-72.
- Bai HX, Giefer M, Patel M, Orabi AI, Husain SZ. The association of primary hyperparathyroidism with pancreatitis. *J Clin Gastroenterol* 2012;46:656-61.
- Debnath NB, Chowdhury A, Maitra S, Ghosh A, Roychowdhury P. Multiple myeloma presenting as acute pancreatitis. *Indian J Gastroenterol* 1999;18:127-8.