A case report of two iatrogenic hypercalcemia incidents following repeated use of calcium sulfate beads in femoral periprosthetic joint infection management

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ABSTRACT

Background: Calcium sulfate beads are frequently used in the management of periprosthetic joint infections (PJIs) because of their effectiveness in local antibiotic delivery and bone void filling. However, repeated use can lead to significant complications, including iatrogenic hypercalcemia. Despite reports of this complication in the literature, the cases in this paper demonstrate a relative lack of awareness among physicians.

Cases: We report two cases of iatrogenic hypercalcemia secondary to repeated administration of calcium sulfate beads in the treatment of femoral PJIs, a cause that was initially unrecognized by the medical team.

Case 1: An 83-year-old woman developed severe hypercalcemia requiring intensive medical management following multiple surgeries for chronic femoral PJI that necessitated implantation of calcium beads for antibiotic delivery.

Case 2: An 81-year-old woman developed recurrent hypercalcemia after multiple administrations of calcium sulfate beads for treatment of her periprosthetic fracture.

Conclusion: These cases highlight the potential risk of hypercalcemia associated with the use of calcium sulfate beads and emphasize the need for careful monitoring of serum calcium levels in such patients. They underscore the importance of multidisciplinary collaboration, which was instrumental in determining the etiology in these cases.

Keywords: Iatrogenic hypercalcemia, Calcium sulfate, prosthetic joint infection (PJI), biofilm, arthroplasty, case report.

Type of Article: CASE REPORT **Specialty:** Orthogeriatrics

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Learning Points of the Article

- To increase physicians' awareness of the postoperative risk of iatrogenic hypercalcemia in patients with prosthetic joint infections managed with calcium sulfate beads.
- To highlight the importance of preoperative calcium level assessment in patients getting these calcium beads.
- To demonstrate the role of regular serum calcium monitoring, particularly preoperatively, in the early detection and prevention of hypercalcemia.

Introduction

Prosthetic joint infection (PJI) is an infection that affects joint prosthesis and surrounding tissues [1]. PJI poses significant risks to patients with mortality rates as high as 20% [2]. Although the overall incidence of PJI in the United Kingdom is relatively low - approximately 1% [3] - it represents a substantial financial burden. This is expected to increase significantly as knee and hip replacements, the two most common arthroplasties, are projected to rise to 40% by 2060 [4].

Multiple treatment strategies exist, including long-term antibiotic suppression, debridement and implant retention (DAIR), one- or two-stage revision arthroplasty, arthrodesis, and amputation [5], each with its own set of indications and complications. Among the adjunctive therapies for these procedures, calcium sulfate beads have emerged as a notable option.

They are used as a carrier for antibiotics and can be applied to both infected and noninfected sites. Their use has expanded across various orthopedic procedures,

ranging from the management of osteomyelitis to the treatment of PJI. Recent studies have reported favorable outcomes in hip and knee PJI revisions when antibiotic-loaded calcium sulfate is utilized [6].

Despite the potential benefits, there remains an underreported risk of iatrogenic hypercalcemia, particularly with repeated administrations. This risk is further heightened when surgical specialists fail to flag this as a potential fallout to the medical team, who would often be looking after these patients post-operatively. This case report aims to illustrate this using two clinical cases while providing insights into prevention and management.

Case Presentations

Case 1

See Table 1 for a timeline of events in both cases. An 83-year-old woman with a left total hip replacement (THR) performed in 2015 developed a hematoma and abscess over the left hip in October 2023. Initial management did not resolve the infection completely, as she developed a discharging sinus over the lower portion of her wound by March 2024. Following a multidisciplinary team discussion, a two-stage revision was planned. The first-stage revision, performed in April 2024, involved the implantation of 20 cc of Stimulan beads (a calcium-based material containing 10.42 g of elemental calcium, Table 2) impregnated with 2 g of vancomycin into the femoral canal and surrounding soft tissues. No calcium level monitoring was performed before and during her hospital stay. She was planned for the next stage in 6-8 weeks and was maintained on prolonged antibiotics as per microbiology guidance.

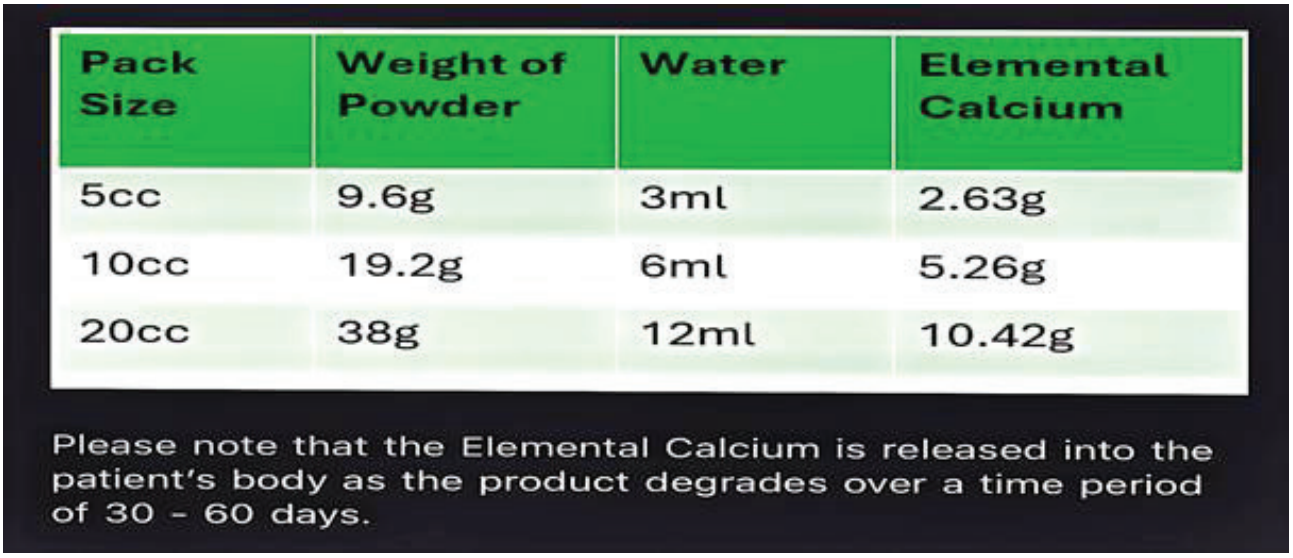
In June 2024, she underwent the second-stage revision, during which another 20 cc of the Stimulan beads were implanted. Postoperative blood tests revealed an elevated calcium level of 2.66 mmol/l, Table 3. Although she remained asymptomatic and below the hospital's treatment threshold, her calcium levels rose to 3.13 mmol/l, Table 3 over the next 48 hours. She subsequently developed symptoms including confusion, lethargy, nausea, vomiting, and malaise.

She was managed with aggressive intravenous hydration, bisphosphonates, and discontinuation of calcium supplements. Given the absence of preoperative

Table 1. *Clinical timeline and outcomes of two cases of iatrogenic hypercalcemia following calcium sulfate bead implantation.*

CASE	DATE / TIMEPOINT	CLINICAL EVENT	INTERVENTION	SERUM CALCIUM (MMOL/L)	OUTCOME
Case 1 (83-year-old female, THR 2015)	Oct 2023	Hematoma and abscess over left hip.	Conservative and surgical	Not measured	Persistent discharging sinus
	Apr 2024 (Stage 1 revision)	First-stage revision with implantation of 20 cc vancomycin-loaded Stimulan beads (calcium-based; 10.42 g elemental Ca)	Surgery	Not measured	Planned for second-stage revision
	Jun 2024 (Stage 2 revision)	Second-stage revision with additional 20 cc Stimulan beads	Surgery	2.66 → 3.13	Developed symptomatic hypercalcemia; managed with fluids, bisphosphonates, and cessation of calcium supplements
	10 days later	Post-treatment follow-up	Supportive	Normalized	Full recovery
Case 2 (81-year-old female with THR 2006)	Feb 2024	Distal femoral periprosthetic fracture treated with ORIF and condylar plating	Surgery	Not measured	Initial recovery
	Apr 2024	Fall → repeat ORIF and removal of metalwork; calcium-based GeneX putty inserted	Surgery	Normal	six-week antibiotic course initiated
	May 2024	Right thigh wound debridement with implantation of 20 cc vancomycin-impregnated Stimulan beads	Surgery	2.69 → 2.81	Asymptomatic hypercalcemia; levels normalized over 4 weeks
	Jun–Jul 2024	Completion of antibiotic therapy and follow-up	Medical	Normal	Full recovery

Table 2. *Showing calcium content of various sizes of Stimulan from the manufacturer.*



NB: *The pack size used in our cases was 20cc.*

Table 3. *Serum calcium levels over the course of treatment in Case 1.*

DATE	TIME	ADJUSTED CALCIUM (MMOL/L)	FLAG
19/06/24	11:09	2.42	
17/06/24	10:18	2.31	
15/06/24	09:39	2.29	
14/06/24	11:05	2.35	
13/06/24	11:21	2.38	
11/06/24	11:21	2.62	High
10/06/24	11:02	2.74	High
09/06/24	10:27	2.63	High
07/06/24	11:55	2.94	High
06/06/24	09:51	3.13	High
05/06/24	11:10	3.11	High
04/06/24	10:53	2.98	High
03/06/24	23:45	2.66	High

Table 4. *Serum calcium levels over the course of treatment in Case 2.*

DATE	TIME	ADJUSTED CALCIUM (MMOL/L)	FLAG
15/06/24	19:18	2.56	
15/06/24	11:33	2.17	Low
14/06/24	11:20	2.43	
13/06/24	13:17	2.19	Low
11/06/24	13:25	2.50	
10/06/24	10:09	2.51	
07/06/24	12:32	2.75	High
06/06/24	10:05	2.70	High
24/05/24	09:53	2.77	High
23/05/24	05:55	2.81	High
22/05/24	09:52	2.70	High
21/05/24	10:15	2.69	High
15/05/24	15:38	2.47	
30/04/24	08:19	2.42	

calcium monitoring, a comprehensive workup for alternative causes of hypercalcemia was undertaken, including assessments for primary hyperparathyroidism, dehydration, malignancy, and multiple myeloma - all of which were negative.

With limited alternative explanations, a review of her surgical notes and discussion with the surgical team prompted a literature search, revealing that calcium sulfate beads can induce hypercalcemia. The company was contacted to confirm the amount of elemental calcium contained in the implants used, and a summary table is included above (Table 2).

Based on the exclusion of other causes, her hypercalcemia was deemed iatrogenic, secondary to the implanted surgical beads. She made a full recovery, with calcium levels normalizing within 10 days following intensive treatment. She was subsequently discharged without complications and remained well on follow-up.

Case 2

An 81-year-old woman with a complex right hip history who had THR back in 2006, sustained 2 periprosthetic fractures of said hip in 2011 and 2024 both of which were treated with open reduction and internal fixation (ORIF) and plating. Two months after the last fracture, she sustained a fracture of the metal work. Following a multidisciplinary team discussion, the decision was made to remove metalwork and repeat ORIF, which happened

in April 2024. GeneX putty, a calcium-based bone void filler, was inserted during the procedure. Postoperative calcium levels remained unremarkable.

She required a 6-week antibiotic course as per infectious disease advise following culture of intraoperative samples. While at the rehabilitation unit, purulent wound discharge and raised inflammatory markers necessitated readmission to the acute hospital. 4 weeks later, she had a wound debridement during which 20 cc of Stimulan beads, Table 2 (impregnated with 1 g of vancomycin) were placed around the metalwork.

Postoperative blood tests within 24 hours revealed a calcium level of 2.69 mmol/l, Table 4. She was monitored closely, being below the hospital treatment threshold. Her calcium levels continued to rise over the following 3 weeks, peaking at 2.81 mmol/l, Table 4. Despite the hypercalcemia, she remained asymptomatic. A full workup for alternative causes - similar to Case 1 - was conducted, yielding negative results. Her calcium levels gradually normalized over 4 weeks without specific intervention. She made a full recovery from both infection and hypercalcaemia.

Discussion

Arthroplasties play a crucial role in pain relief and functional restoration, significantly improving patients' quality of life. However, they can be complicated by various issues, including PJIs, prosthesis fractures, malposition, and dislocations [1].

PJI remains one of the most difficult complications of arthroplasties. Given their often atypical presentation, PJIs require a high index of suspicion for timely diagnosis [7].

Compared to native joint infections, PJIs require a smaller microbial burden and involve the formation of biofilms on prosthetic surfaces, which enables pathogens to evade eradication [8]. Biofilms are complex microbial communities embedded within an extracellular matrix, that on maturation are highly resistant to systemic antibiotics and immune-mediated clearance, making treatment particularly challenging [9,10].

Management of PJI relies on strategies aimed at preventing biofilm maturation while achieving complete pathogen eradication. Current treatment approaches include systemic antibiotic therapy, DAIR—a technique with reported success rates of up to 75% [11,12]—arthroplasty without reimplantation (generally a salvage procedure), one-stage and two-stage arthroplasty exchanges (the latter remaining the gold-standard treatment for PJI), and, in severe cases, amputation when limb salvage is not feasible.

Among these options, DAIR, which combines interventions, has been found to be more effective in surgery-related infections than in hematogenous ones [13]. In both scenarios, shorter symptom duration from onset to treatment correlates with better outcomes [14].

Local antibiotic delivery offers the advantage of having high antibiotic concentrations at the joint site without the systemic toxicity inherent with such levels. This means enhanced biofilm eradication thus improving outcomes.

Local antibiotics may be administered alone or via carriers such as polymethylmethacrylate and bone cement. Non-antibiotic alternatives, such as bacteriophages and ceragenins - still in early development - may prove even more effective in disrupting biofilms [9]. Some of these carriers were fraught with limitations ranging from inconsistent antibiotic release to need for removal post treatment [8].

Therefore, development of resorbable carriers, such as calcium sulfate, hydroxyapatite, bioactive glass, and hydrogels, marked a major advancement - particularly for DAIR and one-stage exchanges, where no return surgery is anticipated, thus revolutionizing PJI management.

Such carriers continuously release antibiotics for several weeks as they are gradually resorbed. Their widespread use has significantly improved PJI treatment outcomes. Among the various carrier options discussed in the literature, calcium sulfate beads (or pearls) are the most extensively studied both *in vivo* and *in vitro*, and they remain the most commonly used [6] as evidenced by our cases.

However, these carriers are not without complications such as persistent wound leakage, heterotopic ossification, and life-threatening hypercalcemia [15].

The multiple use of calcium beads compounds this iatrogenic risk owing to calcium sulfate's high solubility - a pattern consistent with our cases. These findings highlight the importance of vigilant serum calcium monitoring in patients receiving these implantations. One of the key challenges encountered was the absence of preoperative calcium level assessment and limited physician awareness of this potential postoperative complication. Improved recognition of this risk, especially among medical teams not directly involved in the surgery - could enhance perioperative and postoperative protocols, reducing unnecessary investigations when hypercalcemia arises postoperatively. A systematic review of this side effect reported an incidence of approximately 5%, with fewer than 1% requiring active intervention and only one requiring Intensive care admission [15].

Conclusion

Hypercalcemia secondary to calcium sulfate beads can result in severe complications, requiring medical intervention, prolonging hospital stays, and increasing the financial burden of septic joint revisions. Understanding the underlying mechanisms, identifying high-risk patients, fostering medical and surgical team collaboration, and implementing effective perioperative monitoring

strategies are essential areas for further research and heightened clinical awareness.

What is new?

- Iatrogenic hypercalcemia is a notable complication when PJI treatment involves calcium-based implants, especially with repeated use.
- Perioperative protocols should incorporate calcium level assessment to help monitor this risk.

List of Abbreviations

DAIR	Debridement, antibiotic, and implant retention
ORIF	Open reduction and internal fixation
PJI	Periprosthetic joint infection
THR	Total hip replacement

Conflict of interest

There is no conflict of interest regarding the publication of this article.

Consent for publication

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Ethical approval

Ethical approval not required at our institution for anonymous case reports.

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Summary of the Case

No.	Parameter	Summary
1	Patient (Gender, Age)	83 and 81 years, females
2	Final diagnosis	Iatrogenic hypercalcemia secondary to calcium based implants
3	Symptoms	Lethargy, confusion, malaise, asymptomatic
4	Medications	Close monitoring, fluids, bisphosphonates
5	Clinical procedure	None
6	Specialty	Orthogeriatrics