Central Asian Journal of Nephrology
(eISSN 3105-4145)

Case Report

Beyond Iron Repletion: The Hypophosphatemia Risk of Ferric Carboxymaltose

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Received: Mar 17, 2026
Accepted: Apr 04, 2026

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Citation: Alabbasi F, Elraggal M, Alenezi R, Alshaqaq A. Beyond Iron Repletion: The Hypophosphatemia Risk of Ferric Carboxymaltose. Central Asian Journal of Nephrology. 2026;2(2):cajn014. https://doi.org/10.63946/cajn/18335

ABSTRACT

Post-bariatric surgery patients face higher risk of micronutrient malabsorption and often receive intravenous iron like Ferric carboxymaltose (FCM). Recent studies associate FCM with severe (serum phosphate levels < 1 mg/dL) and prolonged hypophosphatemia caused by elevated Fibroblast Growth Factor 23 (FGF23) levels, which reduces phosphate reabsorption in the kidneys via α-Klotho co-receptor. FCM, in particular, can therefore lead to notable and sustained FGF23-mediated hypophosphatemia. We present a case of prolonged and severe hypophosphatemia secondary to fibroblast growth factor 23 (FGF23)-mediated phosphaturia following ferric carboxymaltose (FCM) administration in a post-bariatric surgery patient. This case underscores the complex interplay between intravenous iron therapy, phosphate metabolism, and altered absorption physiology following bariatric surgery. It highlights the need for clinicians to monitor phosphate levels after FCM administration, particularly in high-risk patients such as those with malabsorption.

Keywords: Hypophosphatemia; Fibroblast Growth Factor 23; Ferric Carboxymaltose; Bariatric Surgery; Nephrology; Case Report

Introduction

Iron deficiency anemia (IDA) remains one of the most prevalent diseases globally (1). It has a wide range of symptoms including fatigue, decreased exercise tolerance, and difficulty in concentration (2). Common etiologies include gastrointestinal bleeding, heavy menstruation, pregnancy, celiac disease, atrophic gastritis, inflammatory bowel disease (IBD), bariatric surgery, decreased intake of dietary iron, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), chronic kidney disease (CKD) and malignancy (3).

Although oral iron is the mainstay of treatment, intravenous (IV) iron formulations are preferred for patients with poor tolerance or absorption, including those with IBD, CKD or prior bariatric surgery (4).

Although several IV iron formulations are available, such as low molecular weight iron dextran, ferric gluconate, iron sucrose, ferumoxytol, and ferric derisomaltose (FDI), ferric carboxymaltose (FCM) remains among the most widely used IV iron preparations, largely due to its proven efficacy and tolerability (5).

Emerging evidence linked FCM with severe prolonged hypophosphatemia mediated by elevated Fibroblast Growth Factor 23 (FGF23) levels (6). FGF23 acts on the renal proximal tubules via α-Klotho co-receptor, reducing phosphate reabsorption and causing phosphaturia (7).

The underlying mechanism of increased FGF23 levels and subsequently hypophosphatemia following specifically FCM administration remains unclear, as other IV iron formulation including FDI, iron dextran, or ferumoxytol, do not induce comparable elevation in FGF23 levels. Research has demonstrated that even a single 1000mg dose of FCM results in substantial rise of FGF23 compared to FDI or iron dextran (8).

In this case report, we discuss a patient who developed severe and prolonged hypophosphatemia secondary to FGF23 mediated phosphaturia after recent administration of IV FCM.

Case Report

A 59-year-old woman presented with a 10-day history of worsening bilateral hand stiffness and generalized body aches, accompanied by progressive facial numbness and spasms.

Her medical history included papillary thyroid carcinoma (status post total thyroidectomy with radioactive iodine therapy in 1997), gastric bypass surgery in 2015, osteoporosis managed with vitamin D3 (cholecalciferol 50,000 units monthly) and denosumab (last dose was 6 months before the current presentation), and iron deficiency anemia recently treated with two doses of IV FCM 3 weeks prior to her presentation (750 mg each, administered one week apart). When she received IV FCM, she had a hemoglobin of 9.0 g/dL, iron at 19 mcg/dL, iron saturation at 4%, total iron binding capacity (TIBC) at 450 mcg/dL, and ferritin at 9.03 ng/dL. She reported poor compliance with vitamin D3 and multivitamin supplementation.

On admission, she was afebrile and hemodynamically stable with blood pressure of 104/63 mmHg, heart rate of 72 beats per minute, respiratory rate of 15, and temperature of 36.7 °C. She was alert and oriented, with normal chest and abdomen examination.

Neurological examination revealed a positive Chvostek sign. An ECG confirmed normal sinus rhythm and a QT interval of 467 milliseconds, without any evidence of arrhythmia.

Initial labs demonstrated severe hypocalcemia (5.4 mg/dL) and hypophosphatemia (1.1 mg/dL), with normal albumin (4.2 g/dL), magnesium (1.9 mg/dL) and kidney functions (table 1).

Table 1. Laboratory investigations

Lab test (Unit)	Results on Day 1	Results on Day 12	Results on Day 36-40	Reference range
Calcium (mg/dL)	5.4	6.9	8.7	8.6 - 10.0
Phosphorus (mg/dL)	1.1	2.8	3.2	3.1 - 4.7
Albumin (g/dL)	4.2	4.3	4.4	3.5 - 5.2
Magnesium (mg/dL)	1.9	1.8	1.8	1.7 - 2.4
Potassium (mmol/L)	4.7	4.3	4.2	3.5 - 5.1
Sodium (mmol/L)	142	140	140	135 - 145

Lab test (Unit)	Results on Day 1	Results on Day 12	Results on Day 36-40	Reference range
Chloride (mmol/L)	110	106	105	98 - 107
Bicarbonate (mmol/L)	20	25	21	22 - 28
Creatinine (mg/dL)	0.5	0.5	0.5	0.52 - 1.04
BUN* (mg/dL)	6	10	9	6 - 20
WBC* (K/cumm)	5.9x10^9	N/A	4.9 x10^9	4.0 - 10.0
Hemoglobin (g/dL)	11.8	N/A	12.9	12.0 - 16.0
Platelets (K/cumm)	196 x10^9	N/A	168x10^9	150 - 450
Vitamin D, 25-OH(ng/mL)	32.8	N/A	N/A	20.0 - 50.0
PTH* (pg/mL)	320	N/A	197.1	10 - 65
FGF23* (pg/ml)	457	N/A	60	≤59

BUN: Blood Urea Nitrogen
WBC: White blood count
PTH: Intact Parathyroid Hormone
FGF23: Fibroblast growth factor 23

Parathyroid hormone (PTH) was markedly elevated (320 pg/mL), and FGF23 levels significantly increased (457 pg/mL, reference ≤59 pg/mL). Prior to this presentation, approximately 4 months ago, the patient had essentially normal levels of calcium (9.4 mg/dL) and phosphorus (3.7 mg/dL). Initially, fractional excretion of phosphate using random spot urine was inappropriately elevated (7.24%) in the setting of hypophosphatemia, confirming renal phosphate wasting. 10 days after the initial presentation, a follow up test continued to show persistent renal phosphate wasting with FePO4 of 47.25%. This test was performed when serum phosphate remained low (2.1 mg/dL) whilst on active phosphate replacement.

The patient received intravenous calcium and oral phosphate supplementation throughout her 12-day hospital stay. She was discharged on alfacalcidol, cholecalciferol, calcium carbonate, and sodium phosphate. Given the elevated FGF23 levels and temporal relationship with FCM administration, the diagnosis of FGF23-mediated hypophosphatemia secondary to FCM was established. Serum phosphate levels gradually normalized by day 36 post-admission, while FGF23 levels returned to near-reference range (60 pg/mL). Calcium levels also improved with supplementation (8.2 mg/dl). The patient remained clinically stable with no recurrence of neuromuscular symptoms during follow-up.

Discussion

This case illustrates severe and prolonged FGF23-mediated hypophosphatemia following FCM infusion in a post-bariatric surgery patient. The pathophysiology involves inhibition of FGF23 degradation by FCM, resulting in increased biologically active FGF23. FGF23 via α-Klotho co-receptor primarily acts on the kidneys, inhibiting sodium-phosphate co-transporters NaPi-2a and NaPi-2c in the apical membrane of the proximal tubular cells, thereby increasing renal phosphate excretion (Figure 1) (9).

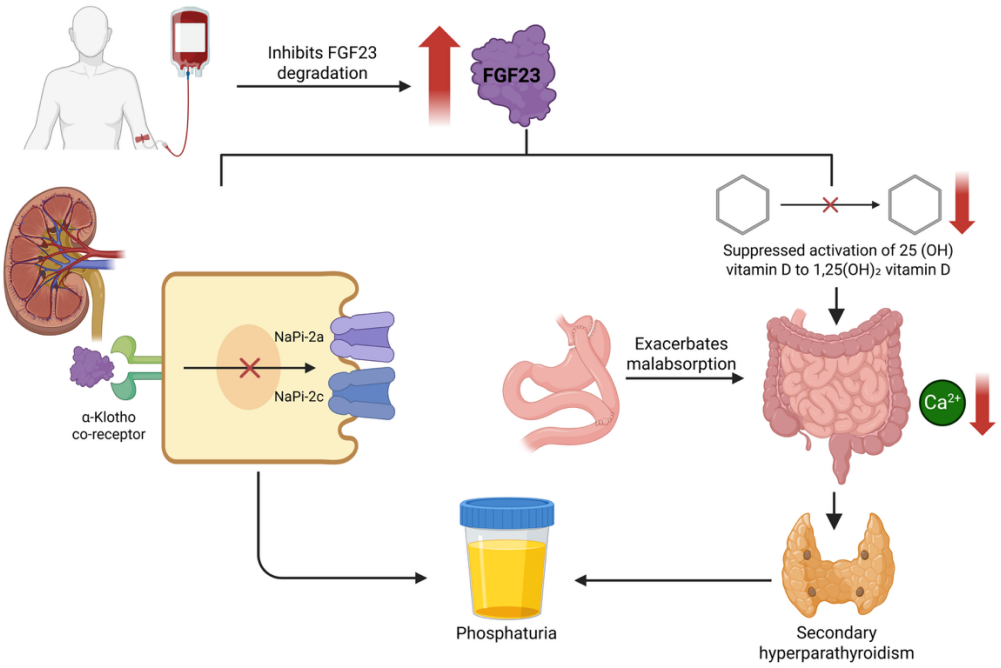

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Figure 1: Mechanism of Hypocalcemia and Hypophosphatemia following Ferric Carboxymaltose in a Bariatric Surgery Patient.

Ferric carboxymaltose inhibits FGF23 degradation, leading to increased biologically active FGF23. Elevated FGF23 acts via α-Klotho co-receptor to suppress sodium-phosphate co-transporters NaPi-2a and NaPi-2c in the apical membrane of the proximal tubular cells, thereby increasing phosphaturia. Elevated FGF23 also suppresses the activation of 25 (OH) vitamin D to 1,25(OH)₂ vitamin D which impairs intestinal calcium absorption. History of bariatric surgery exacerbates this malabsorption. Hypocalcemia leads to elevated parathyroid hormone and secondary hyperparathyroidism. Rise in parathyroid hormone further exacerbates phosphaturia. Abbreviations: FGF23 = Fibroblast growth factor 23, NaPi-2a = Sodium-dependent phosphate transport protein 2A, NaPi-2c = Sodium-dependent phosphate transport protein 2C.

Elevated FGF23 also suppresses the activation of 25 (OH) vitamin D to 1,25(OH)$_2$ vitamin D, leading to hypocalcemia and secondary hyperparathyroidism with further phosphate loss. Bariatric surgery compounds this risk by impairing intestinal absorption of calcium, phosphate, and vitamin D, predisposing patients to metabolic bone disease even before iron therapy (Figure 1) (10). Given the high incidence of IDA in post-bariatric patients and their inability to absorb oral iron, IV iron is a common treatment for this population. Therefore, when these individuals receive IV iron, as illustrated in this case, they may experience more prolonged hospitalizations and extended courses of therapy compared to patients without history of bariatric surgery.

The link between IV iron and phosphorus metabolism was first reported in 1983, when patients receiving daily saccharated iron oxide for 2-5 weeks developed hypophosphatemia within 2 weeks (11). The first documented case of prolonged hypophosphatemia with elevated FGF23 after IV iron polymaltose was in New Zealand in 2009. Since then, multiple studies have confirmed the association of IV iron induced hypophosphatemia (12).

Hypophosphatemia has been reported with several formulations, but FCM is most frequently implicated with hypophosphatemia. A randomized trial of 55 women with iron deficiency anemia from abnormal uterine bleeding compared FCM with iron dextran; only the FCM group developed hypophosphatemia with increased urinary fractionated excretion of phosphate (13). Another randomized trial involving 97 patients with IBD and IDA who were treated with FDI versus FCM. They found that 8.3% of patients receiving FDI developed hypophosphatemia compared to 51% of patients receiving FCM (14).

Additionally, FCM is linked to the longest duration of hypophosphatemia. Some studies have displayed the mean duration of the effect of FCM was around 6 months, with some patients not even reaching normal levels of phosphate after the 2-year study period (15). Similarly, one study revealed that a single dose of FCM 1000mg given to patients with inflammatory bowel disease caused moderate to severe hypophosphatemia in 56.9% of them, with 13.7% continuing to experience persistence after 6 weeks (16).

In our case study, our patient received FCM and experienced a duration of hypophosphatemia up to 36 days until phosphate levels normalized. Patients

with high glomerular filtration rate, low body weight, and underlying nutritional deficiencies are particularly susceptible (17).

Despite that Denosumab has been reported to cause hypocalcemia and hypophosphatemia (18-21), its elimination half-life is approximately 32 days (22), and its serum concentrations decline over 4-5 months (23). This is the reason Denosumab is administered every 6 months for the treatment of osteoporosis, as its effect will be reversed if not given (24). This was also evident by the patient's laboratory investigations 2 months after her last Denosumab dose showing normal calcium (9.4 mg/dL) and phosphorus (3.7 mg/dL) levels.

This case represents the first documented report from Saudi Arabia of prolonged, FGF23-mediated hypophosphatemia following ferric carboxymaltose infusion in a patient with a history of bariatric surgery. The coexistence of post-bariatric malabsorption and IV iron–induced phosphaturia provides a unique insight into the interplay between altered gastrointestinal physiology, phosphate homeostasis, and FGF23 regulation. While hypophosphatemia after FCM has been described in Western populations, regional data from the Middle East are lacking, particularly in the context of post-bariatric patients, which is a demographic with rapidly increasing prevalence in Saudi Arabia. This is demonstrated in recent studies indicating that Saudi Arabia ranks among the countries with the highest rates of bariatric surgery worldwide and continues to experience rapid growth as market estimates project increase in value from USD 66.82 million in 2026 to USD 98.28 million by 2031 (25,26).

Concurrently, the patient exhibited severe hypocalcemia. The underlying mechanism is hypothesized to be secondary to increased FGF23, which leads to reduced calcitriol levels and consequently impairs intestinal calcium absorption. In patients with a history of bariatric surgery, as in our patient, this effect is further intensified due to pre-existing malabsorption. As a result of hypocalcemia, PTH levels increase, triggering secondary hyperparathyroidism. This elevated PTH further exacerbates renal phosphate loss, a phenomenon observed in this patient who demonstrated raised PTH levels. Despite high PTH, persistent low calcitriol and impaired calcium absorption – both consequences of elevated FGF23 – creating a physiological state akin to vitamin D resistance (6,8).

Conclusion

This case highlights the need for proactive monitoring of phosphate levels and individualized iron therapy selection. Clinicians should consider screening serum phosphate prior to and following FCM infusion within 1-week post-infusion, particularly in high-risk populations such as post-bariatric, malabsorptive, or osteoporotic patients. Alternative IV iron formulations, such as ferric derisomaltose or ferumoxytol, should be considered in those patients due to lower risk of FGF23-mediated phosphaturia. Early recognition and management with vitamin D analogues, calcium, and phosphate supplementation are essential to prevent prolonged morbidity.

Acknowledgements

Author Contributions: Conceptualization, F.A., M.E., R.A., A.A.; methodology, F.A., M.E., A.A.; writing – original draft preparation, F.A., M.E., A.A.; writing – review and editing, F.A., M.E., R.A., A.A.; All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Funding: None.

Ethics approval: The study was approved by the institutional review board (Approval number: 25-12-324) on January 4, 2026. Written consent was obtained from the patient.

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