EVIDENCE-BASED MINIREVIEW

# Incidence, mechanism, and consequences of IV iron–induced hypophosphatemia

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**LEARNING OBJECTIVES**

- Define the incidence and risk factors for intravenous iron–induced hypophosphatemia, which is primarily caused by ferric carboxymaltose
- Explain the underlying pathophysiology of intravenous iron–induced hypophosphatemia and how elevations of FGF23 cause renal phosphate wasting
- Recognize signs and symptoms of severe hypophosphatemia to guide appropriate management

## CLINICAL CASE

A 23-year-old woman presents with progressive fatigue and decreased exercise tolerance. Because of suspected iron deficiency from heavy menstrual bleeding, she was previously advised to take oral iron, but gastrointestinal distress limits her adherence. Laboratory testing reveals iron deficiency anemia: hemoglobin 9.8 g/dL and ferritin 4 ng/mL. She is referred for intravenous (IV) iron and gynecologic management of heavy menstrual bleeding. Based on the infusion clinic's formulary, she receives 2 weekly doses of ferric carboxymaltose (FCM), 750 mg each. One week later, she continues to experience fatigue and weakness, and she now describes new muscle aches and brain fog. Her physician initially attributes these symptoms to iron deficiency and counsels that they will soon resolve, but symptoms progress over the next day, leading her to present to the emergency department for further evaluation. Laboratory testing reveals improved hemoglobin, but a serum phosphate of 0.9 mg/dL (normal: 2.6–4.6 mg/dL), prompting inpatient admission.

## Introduction

IV iron therapy is widely used to treat iron deficiency anemia because it is a more effective and faster means of repleting iron stores compared to oral iron.[1] Multiple IV iron formulations exist, but newer agents such as FCM, ferric derisomaltose (FDI), and ferumoxytol (FMX) enable safe administration of high doses of iron in 1-2 infusions. Despite these advances, hypophosphatemia following IV iron administration, which was once considered benign and self-limited, is now recognized as a serious adverse effect of certain IV iron formulations, most notably FCM.[2]

Several randomized trials and a comprehensive systematic review and meta-analysis reported a significantly higher incidence of hypophosphatemia, ranging from 47%-75%, among those treated with FCM versus <10% among patients treated with FDI,[2-4] FXM,[5] and low molecular weight iron dextran (LMWID).[6] Besides causing the highest rate of hypophosphatemia, FCM is also the only formulation associated with severe (<1.0 mg/dl) and prolonged hypophosphatemia that can persist for weeks to several months.[2]

## Pathophysiology

FCM infusion causes acute 3- to 6-fold increases in circulating concentrations of fibroblast growth factor-23 (FGF23), which, along with 1,25-dihydroxyvitamin D and parathyroid hormone (PTH), is one of the main regulators of serum phosphate. The spike in FGF23 causes inappropriate urinary phosphate excretion due to reduced proximal tubular reabsorption of filtered phosphate.[2] As a result, phosphate levels typically reach their nadir approximately 2 weeks following the initial FCM infusion.[3,6,7] FGF23 also decreases circulating concentrations of 1,25-dihydroxyvitamin D, leading

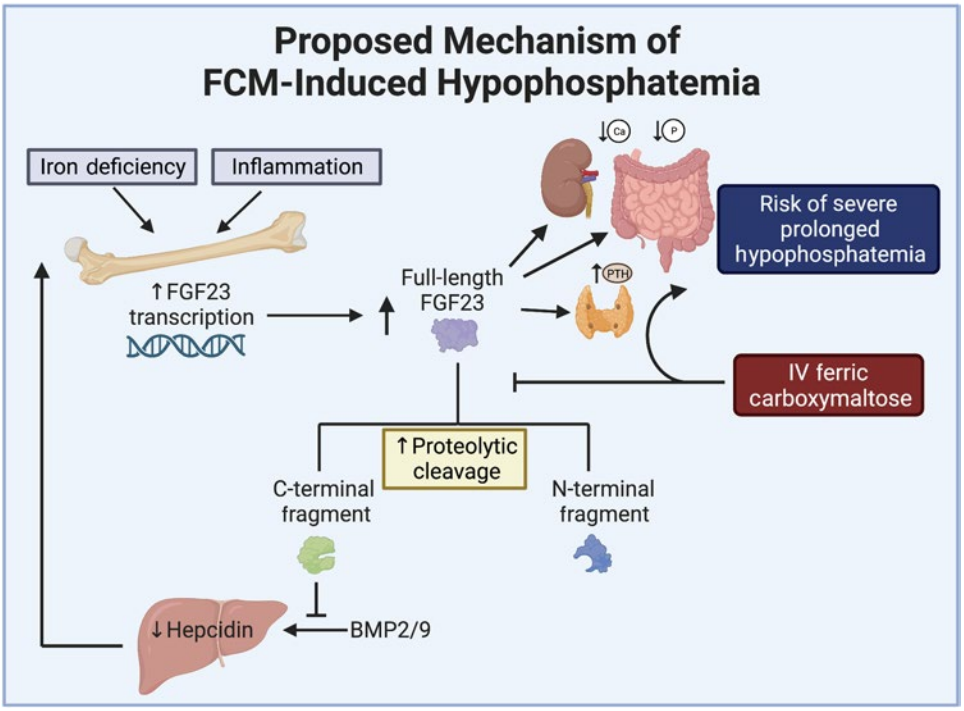


**Figure 1. Proposed mechanism of ferric carboxymaltose (FCM)-induced hypophosphatemia.** Iron deficiency increases FGF23 production, but this is balanced by increased cleavage of FGF23 into its C- and N-terminal fragments that do not affect phosphate homeostasis. Through unclear mechanisms, FCM appears to reduce FGF23 cleavage, resulting in higher levels of full-length FGF23 and, thus, hypophosphatemia. Independent of phosphate homeostasis, C-terminal FGF23 peptides appear to share a negative feedback loop with hepcidin to regulate iron homeostasis by inhibiting bone morphogenic protein (BMP) 2/9-mediated hepcidin production.

to decreased absorption of phosphate from the gut, decreased serum calcium, and secondary increases in PTH. Since PTH also increases renal phosphate excretion, FCM-induced hypophosphatemia is maintained beyond the initial period of FGF23 elevation by a second wave of PTH-mediated renal phosphate wasting.[8]

Growing evidence suggests intricate links between iron and phosphate homeostasis. Iron deficiency and inflammation increase FGF23 transcription and translation in bone, but do not cause hypophosphatemia because increased production of full-length FGF23 is coupled to an increase in intracellular proteolytic inactivation of FGF23 into C- and N-terminal fragments that do not affect phosphate homeostasis (Figure 1).[9] Though the exact mechanism remains unknown, it has been proposed that FCM uncouples FGF23 production and cleavage such that the excessive FGF23 production driven by iron deficiency culminates in higher full-length FGF23 levels upon FCM administration and, thus, hypophosphatemia.[6] The main difference between IV iron formulations—their carbohydrate moieties—may explain their differential effects on FGF23, but this warrants additional investigation.[6]

Independent of phosphate homeostasis that is regulated by full-length FGF23, C-terminal FGF23 fragments also regulate iron homeostasis. Recently, Courbon et al. reported that iron-deficient mice that are unable to augment production of C-terminal fragments had inappropriately increased hepcidin levels that further exacerbated iron deficiency.[10] Conversely, overexpression of C-terminal FGF23 fragments suppressed hepcidin levels by inhibiting bone morphogenic protein (BMP) 2/9 signaling. These novel findings suggest that osteocytes produce C-terminal FGF23 fragments in iron deficiency as part of a negative feedback loop to suppress hepcidin.

## Risk factors and clinical manifestations of hypophosphatemia

In addition to the specific IV iron formulation, other risk factors for FCM-induced hypophosphatemia include normal kidney function, more severe iron deficiency, lower body weight, lower baseline serum phosphate, abnormal uterine bleeding as the etiology of iron deficiency, and repeated doses of IV iron.[2,5,9] Patients with kidney disease are partially protected from FCM-induced hypophosphatemia due to decreased glomerular filtration of phosphate, which limits urinary phosphate excretion.[9] Despite these findings, it is important to emphasize that even patients with no demonstrable risk factors can develop severe and prolonged hypophosphatemia after receiving FCM, and it remains challenging to accurately predict risk, severity, or duration of hypophosphatemia in individual patients.

Acute clinical manifestations of IV iron–induced hypophosphatemia include asthenia, fatigue, and myalgias, all of which reflect tissue-specific energy depletion due to decreased adenosine triphosphate (ATP) production. More severe cases can cause bone pain, myopathy, cardiac arrhythmia, respiratory failure, encephalopathy, and seizures.[9] Anecdotally, many patients report brain fog, perhaps as a consequence of ATP depletion in the brain. Symptoms of hypophosphatemia can mimic those of

iron deficiency anemia, which likely contributes to missed or delayed diagnoses in many affected patients. Chronic hypophosphatemia, particularly in those treated with repeat doses of FCM, can lead to musculoskeletal complications, including osteomalacia and fragility fractures.[7]

## Treatment of IV iron–induced hypophosphatemia

Management of IV iron–induced hypophosphatemia is challenging. Oral and IV phosphate supplementation do not durably sustain normal serum phosphate because of the ongoing renal phosphate leak caused by elevated FGF23 and PTH.[9] Supplementing 1,25-dihydroxyvitamin D can help correct secondary hyperparathyroidism, but evidence to support its use in IV iron–induced hypophosphatemia is limited.[9] Furthermore, both phosphate and 1,25-dihydroxyvitamin D supplementation are known stimuli of FGF23, limiting their effectiveness. Therefore, primary prevention of hypophosphatemia by using iron formulations other than FCM is preferred. When formularies mandate use of FCM, we recommend serum phosphate testing at week 1, prior to administering the second infusion of FCM. If a patient

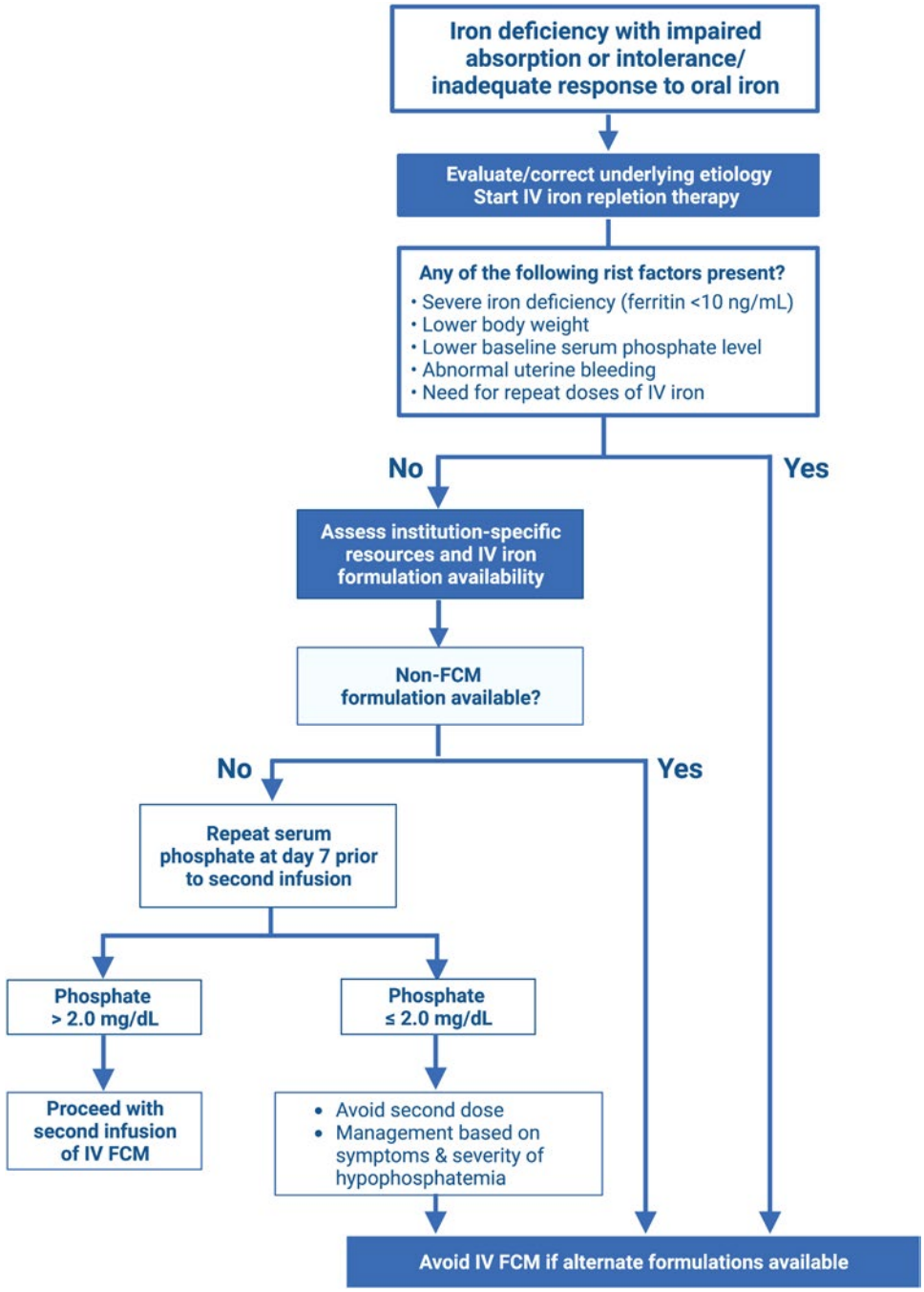


**Figure 2. Algorithm for the selection and safe administration of intravenous (IV) ferric carboxymaltose (FCM) to avoid hypophosphatemia.**

already manifests hypophosphatemia, the second dose should be withheld to prevent exacerbation of hypophosphatemia. Furthermore, we recommend that the risk of hypophosphatemia and its potential consequences be discussed with patients prior to any infusion.

## Conclusions

Despite the high incidence of IV iron–induced hypophosphatemia, many physicians are still unaware and do not recognize acute and long-term complications of FCM. While considering the numerous constraints of modern-day practice, including infusion center availability, drug formulary limitations, and insurance coverage, it is imperative to avoid FCM in patients who require repeated doses (Figure 2). Future studies are needed to investigate why FCM, unlike other IV-iron formulations, disrupts the delicate balance between FGF23 production and cleavage in bone to cause severe hypophosphatemia. An improved understanding of the pathophysiology might help advance therapies to mitigate significant clinical consequences.

## Recommendations

1. FCM should be avoided in the treatment of iron deficiency when alternate IV iron formulations are available, especially in patients who require repeat doses. (Grade 1B)
2. Serum phosphate should be tested at week 1, prior to administering the second infusion of FCM, and the second dose should be withheld in those with serum phosphate ≤2.0 mg/dL. (Grade 1B)
3. Symptoms of fatigue, weakness, myalgias, brain fog, and bone pain following IV FCM should prompt evaluation of serum phosphate, consideration of inpatient therapy if severe hypophosphatemia is confirmed, and avoidance of FCM in the future. (Grade 1A)

### Conflict-of-interest disclosure

Kylee L. Martens: no competing financial interests to declare.
Myles Wolf: equity interests in Akebia, Unicycive and Walden; consultancy: Bayer, Enyo, Jnana, Launch, Pharmacosmos, and Reata.

### Off-label drug use

Kylee L. Martens: Nothing to disclose.
Myles Wolf: Nothing to disclose.


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