

# An Audit of Hypophosphatemia after Intravenous Iron Therapy

## Abstract

### Background

Due to the gastrointestinal side-effects of oral iron supplementation in patients with iron deficiency anaemia, which impairs tolerance - many acute medical and haematology day units provide intravenous iron replacement therapy as day cases. Hypophosphatemia is a frequent side effect following intravenous iron administration, which can persist for weeks or months, is under-recognised in clinical practice and can lead to patients presenting with typical features to the emergency departments.

### Aim

We designed an audit to measure the incidence of symptomatic hypophosphatemia after intravenous iron therapy to develop monitoring, prevention, and treatment strategy in a secondary care hospital setting.

### Methods

We audited a convenience sample of consecutive patients who attended an acute day-care assessment unit for intravenous (IV) iron infusion (ferric carboxymaltose). All patients had serum phosphate levels checked after IV iron infusion at different intervals, from 1- 6 weeks. The cohort was divided into two groups based on the occurrence of hypophosphataemia - early (1-3 weeks) and late (>3-6 weeks).

### Results

We included 35 patients referred from primary care, gastroenterology, gynaecology, and acute internal medicine. 19 (55%) developed hypophosphatemia after receiving a single IV iron infusion and almost 100% after more than one dose. Hypophosphatemia in some patients lasted up to 12 weeks.

### Conclusion

Hypophosphatemia was frequent after a single dose and almost universal after multiple doses of IV Iron, which can persist for many weeks. Clinicians prescribing ferric carboxymaltose (Ferinject<sup>®</sup>) should be aware of hypophosphataemia, which could be mild, moderate, or severe and can last for months.

### Keywords

Iron deficiency anaemia, intravenous iron therapy, hypophosphataemia

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## Introduction

Iron deficiency is a significant cause of anaemia affecting patients with chronic kidney disease, inflammatory bowel disease, intestinal malabsorption syndromes, and women with heavy menstrual bleeding. Oral iron supplementation is the standard first-line therapy for iron deficiency. However, it is associated with gastrointestinal side effects and low bioavailability, often leading to non-adherence to treatment.[1] Hence, the parenteral is frequently the preferred route, as this allows the administration of large amounts of Iron (ferric carboxymaltose) 1000 mg in one infusion.[2]

Fibroblast Growth Factor 23 (FGF23) is a peptide secreted by osteoclasts and osteoblasts in response to raised phosphate levels, which limits phosphate reabsorption in the renal tubules, thus maintaining phosphate homeostasis. The carbohydrate moieties in some of the iron preparations (e.g., carboxymaltose in Ferinject) have been implicated in altering the FGF23 protein, thereby inhibiting its degradation[3]. High levels of FGF23 can inappropriately decrease phosphate reabsorption in the proximal renal tubules, even in the presence of continued low serum phosphate levels, leading to renal wasting of phosphate and hypophosphataemia. Additionally, FGF23 inhibits the production of calcitriol, which is necessary for phosphate absorption in the intestines [4].

Hypophosphatemia is defined as a serum phosphate level of less than 2.5 mg/dL (0.8 mmol/L) in adults. Phosphate is critical for a vast array of cellular processes, and it is one of the significant components of the skeleton, providing mineral strength to the bone. Given its widespread role in nearly every molecular and cellular function, aberrations in serum phosphate levels can be highly impactful. Phosphate plays an essential role in the organism, and hypophosphatemia, especially when phosphate plasma level <1 mg/dL (0.32 mmol/L), can lead to cardiac arrhythmias or arrest. Severe

hypophosphatemia is also associated with various complications, including fatigue [5], seizures [6], osmotic demyelination syndrome [7], myocardial depression [8], ventricular tachycardia [9], proximal myopathy [10], rhabdomyolysis[11], and haemolytic anaemia [12], metabolic encephalopathy and contribute to the development of central and extrapontine myelinolysis [13].

Hypophosphatemia is a frequent but under-recognised side effect following intravenous iron administration, which can persist for weeks or months. The likely mechanism for hypophosphatemia is a direct toxic effect on proximal tubular cells and elevated FGF23 or suppressed 1,25(OH)<sub>2</sub>D levels. Patients with pre-existing hyperparathyroidism and vitamin D deficiency may be particularly susceptible, for example, patients following kidney transplantation or with gut malabsorption. Conversely, patients with chronic or end-stage kidney disease may be at reduced risk due to reduced tubular phosphate excretion and pre-existing chronically upregulated FGF23. Repeated iron infusions and associated hypophosphatemia can result in osteomalacia, and phosphate should be supplemented if there is severe, prolonged, or symptomatic hypophosphatemia.

## Methods

We conducted this single-centre clinical audit at a large inner-city teaching hospital in London, with an average daily emergency room attendance of 440 patients and around 75 patients needing admission to the acute medical unit. Data was collected for the audit after verbal consent from the patients. Patients were followed up by their primary teams. The audit was registered with the Hospital Audit and Quality Improvement team.

We collected a convenient, consecutive sample data set of patients who attended our acute day-care

assessment unit for an iron infusion, and all patients received ferric carboxymaltose infusion. Patients were given 1 or 2 doses of iron infusion depending on their iron profile and calculated dose.

#### Blood tests

Routine blood tests, including phosphate levels before iron infusion, are standard practice in our unit. Patients were followed up 12 weeks after receiving the iron infusion, and blood tests were undertaken between 1-6 weeks after the IV Iron therapy. The timing of sample collection varied from 1 week to a few weeks after the infusion. Patients who came for their second dose infusion after a week had their phosphate level checked before their second infusion.

#### Analysis

We reviewed data as hypophosphatemia in an immediate period up to 3 weeks after infusion, and then low phosphate levels lasting beyond three weeks were monitored further with repeat blood tests. Subsequent blood tests were done only to monitor persistent hypophosphatemia. We analysed the data separately for patients based on whether they had a single dose of IV iron or more doses of IV Iron. We further analysed the data for patients for whom Vit D levels were available and were done within three months before the iron infusion. Vitamin D deficiency was described as serum levels below 50 nmol/L.

### Results

#### *Population*

Our audit included (n=35) patients referred from primary care, gastroenterology, gynaecology, and acute medicine. Demographics are presented in Table 1; the majority were women. One patient received three doses, 9 received two doses over two weeks, and the rest (n=25) a single dose of IV iron.

All patients had serum phosphate levels within the normal range > 0.8mmol/L before iron infusion. Nineteen patients (54%) developed hypophosphatemia after IV iron infusion, including 5 developing severe hypophosphatemia, with levels dropping below <0.32mmol/L.

#### *Single dose*

Among patients receiving a single dose of IV Iron, 36% developed hypophosphatemia. Hypophosphatemia improved over 4-8 weeks without any replacement, but one had a lasting low phosphate level of 0.69 mmol/l at 12 weeks and received oral phosphate replacement (Fig 1).

#### *Multiple doses*

Of the ten patients who returned for a second dose of iron infusion after one week, only one had low phosphate (0.67mmol/l). All ten patients developed hypophosphatemia over 12 weeks of monitoring (Fig 2). Except for one patient whose phosphate normalised after three weeks of IV iron, the remaining nine patients had lasting severe hypophosphatemia for over eight weeks. Three patients had persistent hypophosphatemia even at 12 weeks and were given oral phosphate replacement. (Fig 3)

#### *Vitamin D*

Of a subset of 15 patients with recorded vitamin D levels, four took Vit D supplements, and ten had levels below 50 nmol/l. Patients with adequate levels of Vit D also developed hypophosphatemia, as shown in (Fig 4).

### Discussion

Our audit highlighted that over half of the patients with normal baseline phosphate levels risk developing significant hypophosphatemia following IV iron therapy. The risk appears to be higher after multiple doses, and our data suggest that concurrent

low Vit D might contribute to hypophosphatemia development.

IV iron is an established mode of treatment in patients with iron deficiency who are intolerant to oral iron replacement. Many ambulatory, acute medical units or day units increasingly provide this therapy outside established haematology specialist centres. Many units have protocols which include baseline assessment of serum phosphate and often vitamin D levels as part of the pre-assessment. Symptoms of mild hypophosphataemia (fatigue) often overlap with iron deficiency symptoms, and all our patients reported tiredness and muscle fatigue. In patients with phosphate

deficiency, conservative therapy includes dietary advice, and supplementation is only offered for moderate to severe deficiency. In our cohort, oral supplements were offered to those with persistent hypophosphatemia beyond eight weeks.

A systematic review [14] of hypophosphataemia in adult Iron deficiency anaemia patients receiving IV Iron in the USA, suggested that most studies may have underestimated the occurrence of hypophosphatemia and its clinical consequences due to the short duration of dosing regimens and follow-up, inconsistent and infrequent measurement of serum phosphate, inconsistent definitions of hypophosphatemia, and overlap of symptoms of hypophosphatemia and anaemia. Consequently, the long-term effects of hypophosphatemia or repeat IV Iron dosing may not have been considered in most trials.

In contrast to the "asymptomatic" hypophosphatemia reported in trials, case reports

demonstrate that IV Iron-induced hypophosphatemia may be a serious clinical consideration, including short-term consequences of severe muscle weakness and fatigue and long-term concerns of fractures and bone deformities due to hypophosphatemic osteomalacia in patients undergoing repeat IV

Iron therapy.[13] Profound or sustained hypophosphatemia can occur in some patients lasting up to 12 weeks who receive multiple doses of Iron. Despite several case reports, most healthcare professionals may not be fully aware of this side effect, although it is included in references such as the British National Formulary. Patients are not routinely counselled or monitored for this possible side effect.

**We recommend that;**

1. Screening for IV iron should include baseline phosphate, vitamin D levels and dietary deficiency or malabsorption states
2. Counselling should include a prompt for patients to report the persistence of symptoms of fatigue and tiredness persisting after iron replacement, along with guidance for dietary supplementation of phosphate-rich foods
3. Professionals should be aware of the risk of repeated iron infusions and associated moderate to severe hypophosphatemia that can result in osteomalacia, and phosphate supplementation should be considered if there is severe, prolonged or symptomatic hypophosphatemia.
4. Longer monitoring of serum levels should be offered in patients at increased risk of hypophosphataemia or associated deficiencies.

Table :1 Population demographics

Age (N= 35)	Average - 51.8 years (Youngest -19 years and oldest -88years)
Gender	F – 24 (68.5 %) M- 11 (31.4%)
Baseline serum phosphate values	Male - (median 0.94, IQR 0.195) Female -(median 1.10, IQR 0.195)
Vit D levels (N= 15)	Median 30.5, IQR 30

Fig:1 Phosphate levels after a single dose of iron infusion

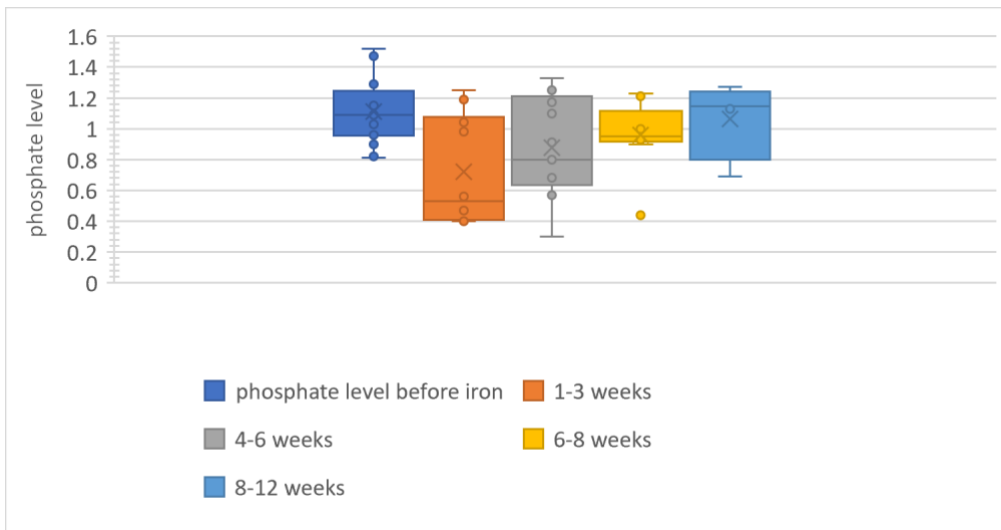


Fig: 2 Phosphate levels after 2 doses of iron infusion

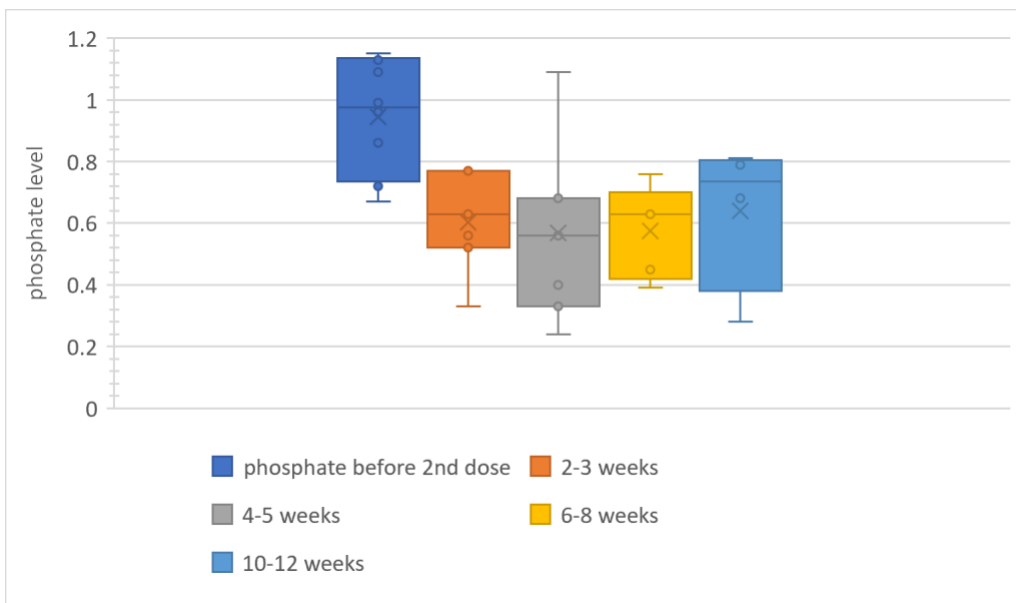


Fig:3 Phosphate levels after iron infusion in patients with Vit D levels

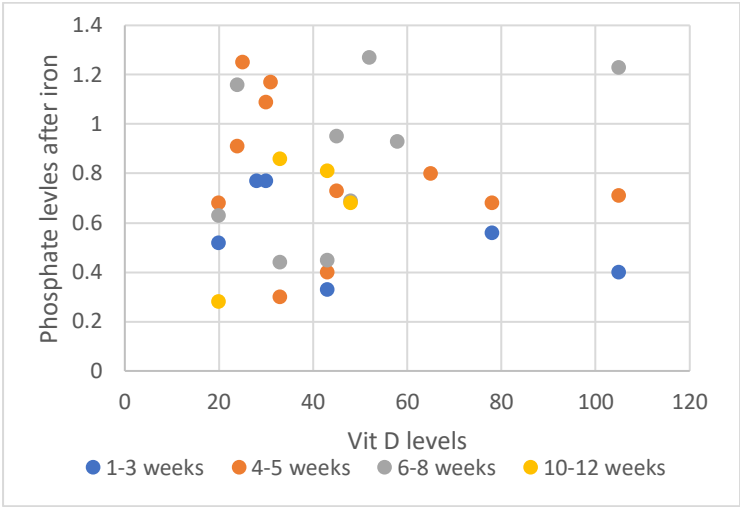
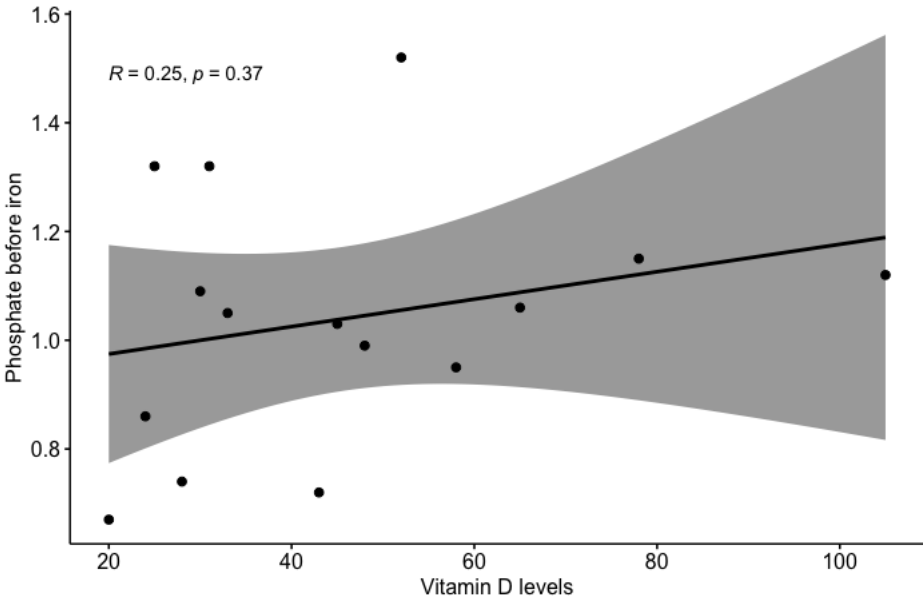


Fig:4 Phosphate levels after iron infusion along with Vit D levels



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