REVIEW

Hypophosphataemia, fibroblast growth factor 23 and third-generation intravenous iron compounds: a narrative review

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Abstract
Third-generation intravenous (i.v.) iron preparations are safe and efficacious and are increasingly used in the treatment of iron-deficiency anaemia. Hypophosphataemia is emerging as an established side-effect following the administration of certain compounds. Symptoms of hypophosphataemia can be masked by their similarity to those of iron-deficiency anaemia and both acute and chronic hypophosphataemia can be detrimental. Hypophosphataemia appears to be linked to imbalances in the metabolism of the phosphatonin fibroblast growth factor 23. In this narrative review, we discuss the possible pathophysiology behind this phenomenon, the studies comparing third-generation i.v. iron compounds, and the potential implications of the changes in fibroblast growth factor 23 and hypophosphataemia. We also present an algorithm of how to approach such patients requiring i.v. iron in anticipation of hypophosphataemia and how the impact related to it can be minimized.

Keywords: ferric carboxymaltose, ferric derisomaltose, ferumoxytol, fibroblast growth factor 23, hypophosphataemia, intravenous iron, iron-deficiency anaemia, safety.

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Introduction

Iron is an essential trace mineral necessary for life due to its involvement in several important metabolic processes. Given the importance of iron in oxygen transfer and energy production, it is not surprising that iron-deficiency anaemia (IDA) is a major cause of disability, linked to physical and cognitive decline, worsening prognosis in chronic disease, and reduced quality of life.¹ The aetiology varies according to geographic location; however, the causes can be broadly divided into blood loss, increased iron demand, and decreased absorption, which can be related to both malabsorption and chronic disease. Additionally, certain medications can contribute to the development of IDA (e.g. non-steroidal anti-inflammatory drugs, antithrombotic agents, angiotensin-converting enzyme inhibitors, proton-pump inhibitors).² As IDA is associated with chronic diseases such as inflammatory bowel disease (IBD), chronic kidney disease (CKD), cancer and chronic heart failure, it can affect healthcare economics and rationing.² It is therefore important that safe and cost-effective methods of addressing this issue are available to clinicians.

A number of guidelines governing the management of IDA both in the general population and within specific diseases have been published and suggest an initial trial with oral iron preparations; however, they also advocate intravenous (i.v.) iron where there is intolerance or non-adherence to oral iron or where the response is not adequate.³,⁴ In certain cases, i.v. iron is recommended as first line such as in patients dependent on haemodialysis or those with symptomatic chronic heart failure with reduced ejection fraction, moderate-to-severe IBD with significant anaemia, active IBD (where oral iron may exacerbate symptoms in the gut), obstetrics (both pre-partum and post-partum depending on severity and symptomatology of anaemia), and historically pre-operatively where the interval between diagnosis and surgery is less than 2 weeks.³,⁵–⁸ However, in the latter case, a recent multicentre double-blinded randomized placebo-controlled trial (n=487) has cast doubt on its use prior to major abdominal surgery.⁹

Oral iron is inexpensive, easy to administer and, in certain cases, effective.²,⁴,¹⁰ However, adherence and long-term tolerability are limited due to side effects and absorption is affected by states of chronic inflammation due to a persistent rise in IL-6.
and hepcidin or due to interactions with other drugs. As such, the use of i.v. iron has gained popularity and has necessitated the development of safe and efficacious compounds.

Intravenous iron has been used to treat IDA since the early 1940s; the first generation of these compounds (e.g. high-molecular-weight iron dextran) is scarcely used due to relatively high rates of anaphylactic episodes. This led to the development of second-generation i.v. iron compounds (e.g. low-molecular-weight iron dextran, iron sucrose), which coincided with the use of erythropoiesis-stimulating agents. Second-generation i.v. iron compounds are associated with a significantly lower incidence of anaphylaxis and hypersensitivity reactions; however, their use is limited by constraints on dose and duration of infusion due to the potentially high amount of labile iron release. Labile iron toxicity and the associated potential oxidative stress raised concerns on the susceptibility to infection, worsening cardiovascular prognosis and iron overload. Third-generation i.v. iron compounds were hence developed (Table 1), allowing rapid, potentially complete repletion dosing in a single sitting without the toxicity issues related to older preparations. These properties are a result of their tightly packed iron-carbohydrate cores, which allow for a controlled release of ‘free or catalytic’ iron and less generation of non-transferrin-bound iron and are beneficial in terms of healthcare economics, a reduction in the use of erythropoiesis-stimulating agents, and a potentially decreased cardiovascular risk. Nonetheless, there are unique physicochemical differences between third-generation i.v. iron preparations as reflected by their safety profiles. Despite the low rates of hypersensitivity reactions, a distinct noted difference is the incidence of hypophosphataemia and the potential resultant impact on other bone markers.

In this narrative review, we focus on the links between iron and phosphate metabolism, the most recent comparative studies between third-generation i.v. iron compounds, the important role of fibroblast growth factor 23 (FGF23), and the impact of hypophosphataemia on the patient. We also present an algorithm that can be used in patients requiring i.v. iron in anticipation of potential hypophosphataemia.

**Methodology**

In order to identify studies relevant to the topic, a literature search was conducted in October 2020 that covered the third-generation i.v. iron literature published since 2003. The search was repeated in December 2020 to ensure no missing literature upon review of the manuscript. Information was obtained through PubMed using “ferric carboxymaltose”, “iron isomaltoside”, “ferric derisomaltose” and “ferumoxytol” as keywords in the title/abstract, and 900 articles were identified. The brand names of compounds were not used in

**Table 1. Third-generation i.v. iron preparations.**

| Characteristics of currently available third-generation i.v. iron formulations | Ferumoxytol | Ferric carboxymaltose | Ferric derisomaltose\(^a\) |
|---|---|---|---|
| Maximum single dose | 510 mg | 1000 mg | 20 mg/kg (500 mg if bolus) |
| Minimum administration time (minutes) | 15 | 15 | 15 |
| Replacement dose possible in a single infusion | No | Yes | Yes |

| Comparison of physicochemical characteristics and pharmacokinetics of third-generation i.v. iron formulations |
|---|---|---|---|
| Molecular weight (kDs) | 185 | 150 | 150 |
| Carbohydrate ligand | Polyglucose sorbitol carboxymethyl ether | Carboxymaltose | Isomaltoside |
| Relative stability of iron carbohydrate complex | High | High | High |
| Reactivity with transferrin | Low | Low | Low |
| Relative labile iron release | Low | Low | Low |
| Plasma half-life (hours) | 15 | 7–12 | 20 |

\(^a\)Ferric derisomaltose also exists in a 5% compound form with the brand name Diafer\(^a\), which has different dose adjustments as relevant. We advise to always refer to local guidelines and the available literature. Commercial names and doses may vary according to countries/regions.

Adapted from: Bhandari et al.\(^2\)
the literature search. A total of 55 articles discussing phosphate concentrations were considered relevant to the topic and were reviewed; further studies that were identified in those articles were also reviewed and hence included.

Iron metabolism and phosphate – what is the link

Phosphorous – in the form of inorganic phosphate (PO$_4^{3-}$) – is essential for several cellular functions, including structure, energy production, metabolic pathways, and signalling. The majority of phosphate (85%) exists within the skeleton and is intracellular. A complex system involving diet, multiorgan crosstalk, hormones, and other factors co-ordinates phosphate regulation, maintaining serum levels within a normal range of 0.8 to 1.2 mmol/L (2.48–4.65 mg/dL) for adults. This is governed by the rate of absorption of dietary phosphate in the gut, reabsorption and excretion of phosphate by the kidneys, and the flux of phosphate from the skeletal and other extracellular pools.

Dietary phosphate absorption in the gut occurs via passive paracellular diffusion and by active cell-mediated transport of phosphate, involving the sodium–phosphate (NaPi)-2b cotransporter on the luminal side of the enterocyte (Figure 1). This cotransporter is regulated by dietary phosphate and calcitriol (1,25-dihydroxyvitamin D (1,25(OH)$_2$D)) concentrations, and there is increasing evidence on the importance of the phosphatonin FGF23. Absorbed phosphate recycles within the extracellular fluid and skeletal pools as necessary and is freely filtered through the glomerulus and reabsorbed via the renal NaPi type 2 cotransporters, NaPi-2a and NaPi-2c, which are expressed on the luminal side of the proximal tubular epithelial cells. Kidney phosphate reabsorption, like gut absorption, is affected by the concentrations of FGF23 and dietary phosphate as well as by parathyroid hormone (PTH) action. In order for phosphate levels to be maintained, urinary phosphate excretion must therefore be proportional to oral intake and intestinal absorption. Renal phosphate excretion is stimulated by an interplay between FGF23 and PTH, both of which increase in response to increased serum phosphate.

FGF23, a bone-derived hormone, has been shown to be intricately involved in iron phosphate and vitamin D metabolism. FGF23 regulates phosphate handling and is secreted as a response to increased calcitriol, PTH, hyperphosphataemia, or oral phosphate intake. It is synthesized and secreted mainly by osteocytes and acts on the kidneys through a reduction of activity of the NaPi cotransporter in the proximal tubules and inhibits the synthesis of calcitriol, thereby leading to phosphaturia (Figure 1). Moreover, increasing levels of FGF23 may eventually amplify PTH synthesis. In order for the described effects to occur, FGF23 needs to bind to FGF receptors in the presence of membrane-bound klotho, which serves as a coreceptor, with such receptors being present in the kidneys, parathyroid glands, and choroid plexus. Two detectable forms of FGF23 exist in the human body: intact FGF23 (iFGF23), which is mostly responsible for these actions, and cleaved FGF23 (cFGF23). FGF23 levels increase as CKD progresses as a ‘normal’ physiological response to maintain phosphate homeostasis but at the expense of vitamin D deficiency. In addition, hypoxia and inflammation increase total FGF23; however, a satisfactory compensatory mechanism of increased cleavage rate exists in order to maintain equilibrium. Experimental data suggest that iron deficiency increases FGF23 expression through action on hypoxia-inducible factors (HIFs) HIF1α and HIF1b, which in turn affect both induction and transcription – this increase in FGF23 is accompanied by an increased cleavage of iFGF23 to cFGF23 (therefore, a preserved iFGF23 to cFGF23 ratio). However, an imbalance between the two (iFGF23 > cFGF23), as exhibited in autosomal dominant hypophosphataemic rickets, can invariably lead to hypophosphataemia; a similar ‘two-hit hypothesis’ appears to be the answer behind i.v. iron-induced hypophosphataemia (Figure 2).

Initial theories supported the notion of transient asymptomatic hypophosphataemia with ferric carboxymaltose (FCM) secondary to a rapid increase of erythropoiesis causing increased phosphate uptake. With an increasing number of reports in the literature related to the topic, suggestions of a drug-specific and not class-specific side-effect appeared. Indeed, deferasirox (an iron chelator) has been previously associated with hypophosphataemia due to Fanconi’s syndrome as a possible mechanism. These phenomena led to the landmark randomized controlled trial (RCT) by Wolf et al., where 55 women with idiopathic secondary to heavy uterine bleeding received either low-molecular-weight dextran or FCM. The findings added support to the theory of increased FGF23 transcription due to IDA with a satisfactory compensatory cleavage mechanism (increased cFGF23/normal iFGF23). Alleviation of iron deficiency caused a reduction in cFGF23 within 24 hours (80%) in both groups; however, ifFGF23 increased only in the FCM group. This increase in iFGF23 was coupled with a transient asymptomatic reduction in serum phosphate in ten women in the FCM group, accompanied by increased phosphaturia (expressed as fractional excretion of phosphate in the urine (FEPi %), leading to a reduction in calcitriol and an increase in PTH. The authors concluded that IDA represents a state of increased transcription and cleavage of FGF23, which is alleviated upon administration of iron; however, it is possible that the carbohydrate ligand associated with FCM inhibits the cleavage of iFGF23, leading to renal phosphate loss and hypophosphataemia.

Comparing iron preparations

A systematic review focused on trials involving iron preparations that were licensed in the United States at the time of publication (FCM, ferumoxytol, low-molecular-weight iron dextran, iron sucrose); 40 articles were included in the analysis (19 RCTs, 10 observational studies, 11 case reports). Hypophosphataemia rates were found to be 0.0–92.1% for FCM, 0.0–40.0% for iron sucrose, 0.4% for ferumoxytol and
0.0% for low-molecular-weight iron dextran. All of the RCTs in the systematic review reported hypophosphataemia to be transient, while the case reports included (exclusively involving FCM) described severe fatigue associated with acute hypophosphataemia and osteomalacia and fractures in cases of chronic hypophosphataemia linked to repeated i.v. iron infusions. The authors reported that hypophosphataemia was not strictly defined and was not adequately followed-up in terms of symptoms or duration in a number of studies. Trials related to ferric derisomaltose (FDI) were not included in this systematic review as, at the time of the literature search, the FDI preparation was not available in the market in the United States. A later systematic review and meta-analysis focusing solely on RCTs comparing i.v. iron preparations included eight studies (n=5989) and reported on outcomes relevant to FCM, FDI, low-molecular-weight iron dextran, iron sucrose, and ferumoxytol. The results of a Bayesian network meta-analysis highlighted an increased incidence of hypophosphataemia associated with FCM use, with no significant differences estimated for the comparisons between FDI, iron sucrose, low-molecular-weight iron dextran, and ferumoxytol. A systematic review and meta-analysis specific to FCM and FDI including 42 clinical trials
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(36 RCT, 6 observational studies; n=11,700) concluded that FCM induces a significantly higher incidence of hypophosphataemia and significantly decreases serum phosphate compared to FDI (47% (95% CI 36–58) versus 4% (95% CI 2–5) and 0.40 versus 0.06 mmol/L, respectively). Through meta-regression analysis, the authors identified that the severity of iron deficiency (low serum ferritin, low transferrin saturation) and better kidney function were significant predictors of hypophosphataemia. A further pooled analysis of 45 interventional trials including FCM (n=15,080) confirmed the association between FCM and hypophosphataemia incidence as 41.4% of participants displaying mild hypophosphataemia at any point of the trials included (n=2847, PO₄³⁻ concentration <0.8 mmol/L) and 0.7% (n=49) suffering from severe hypophosphataemia (PO₄³⁻ concentration <0.3 mmol/L). Such results highlight that hypophosphataemia is possibly a drug-specific side-effect that is not necessarily exhibited uniformly by all other i.v. iron compounds.

In total, currently four RCTs have taken place comparing third-generation i.v. iron compounds (n=2268), more specifically comparing FCM with ferumoxytol and FCM with FDI in patients with IDA. A large RCT, primarily assessing safety, randomized 1997 patients with IDA intolerable or refractory to oral iron to receive FCM (n=1000; at a dose of 2 × 750 mg) or ferumoxytol (n=997; at a dose of 2 × 510 mg). Despite a comparable low rate of hypersensitivity reactions, hypophosphataemia incidence at second week post infusion (<0.64 mmol/L) was significantly greater with FCM compared to ferumoxytol (38.7% versus 0.4%). This persisted through to week 5, with a significant difference in FEPi % at both weeks 2 and 5 (p<0.001 and p<0.05, respectively). A prespecified nested physiological subanalysis (FCM, 98; ferumoxytol, 87) monitored the participants’ FGF23, calcitriol, and PTH levels at weeks 1, 2, and 5. A significant increase in iFGF23 was seen in patients that received FCM and this was reflected in the increased FEPi % and PTH and reduced serum phosphate and calcitriol concentrations. The nadir of hypophosphataemia was
noted with FCM at approximately 2 weeks post infusion.\textsuperscript{38} These findings supported those of the earlier study by Wolf et al.\textsuperscript{39} with an increase in iFGF23 following FCM administration and a trend for a comparable decrease in cFGF23 irrespective of iron used, highlighting the likelihood of hypophosphataemia being caused by an imbalance in cleavage of FGF23.\textsuperscript{30} Similarly, two recently published RCTs (collectively known as PHOSPHARE-IDA) compared FCM (2 × 750 mg) with FDI (1 × 1000 mg) in 245 patients with IDA.\textsuperscript{36} A greater incidence of hypophosphataemia was seen with FCM at day 35 post infusion compared to FDI (FCM, 43.0%; FDI, 0.9%; \(p<0.001\)); iFGF23 was increased compared to cFGF23, with FCM resulting in a significant increase in PTH and renal phosphate excretion and a significant decrease in calcitriol.\textsuperscript{34} However, these three studies are limited by the fact that the comparison between drugs was performed using different dosing regimens and one could argue that, by doing so, the impact of a single iron infusion is not fully examined and the findings may not hence be comparable. A smaller-scale RCT involving 26 women who were iron deficient due to heavy uterine bleeding examined the impact of a single i.v. iron infusion (max 20 mg/kg up to 1000 mg) both on bone and cardiac metabolism, with the incidence of hypophosphataemia (\(<0.64 \text{ mmol/L}\)) being investigated as the primary endpoint.\textsuperscript{37} A significantly greater incidence at any time point was seen following administration of FCM compared to FDI (FCM, 9/12 (75%); FDI, 1/13 (8%); \(p=0.001\)), which was also associated with a significant decrease in calcitriol (\(p<0.001\)) and a significantly greater FEPi % at day 7 (\(p<0.05\)).\textsuperscript{37} No impact to cardiac or other bone metabolism marker was noted; however, the study was not powered to reach conclusions and the authors concluded that the absence of change could potentially be related to the small numbers. Research on the topic of iron deficiency indicates that a high rate of hypophosphataemia can be associated with abnormal uterine bleeding and, as such, this poses a confounding factor both in this study as well as in the PHOSPHARE-IDA studies, where most participants were women with anaemia associated to heavy uterine bleeding.

Evidence suggesting that hypophosphataemia is more strongly associated with FCM also comes from observational studies in patients with gastrointestinal disease comparing FCM and FDI. Single-dose FCM and FDI were compared in 106 patients with IBD (FCM, 52; FDI, 54).\textsuperscript{39} There was a significantly higher incidence of hypophosphataemia with FCM at weeks 2 and 6 (\(p=0.001\) and \(p=0.0013\), respectively) while the incidence of moderate-to-severe hypophosphataemia was significantly higher at week 2 following infusion with FCM.\textsuperscript{39} Bager et al.\textsuperscript{40} reviewed data from 231 patients treated with FCM and/or FDI over a 3-year period from a general gastroenterology clinic. They noted an increased hypophosphataemia (\(<0.64 \text{ mmol/L}\)) incidence rate with FCM (64 versus 9; \(p<0.001\)) while 13 patients developed severe hypophosphataemia (\(<0.32 \text{ mmol/L}\)) 2 weeks following FCM infusion (\(p=0.001\)). The drop in phosphate was more significant at weeks 2 and 5 when comparing FCM to FDI (\(p<0.001\)).\textsuperscript{40} The study did not collect data on symptomatology, duration of hypophosphataemia, or impact on bone markers. The electronic records of 81 patients were reviewed following infusion with either FDI or FCM; where available, paired samples of bone markers (iFGF23, cFGF23, calcitriol, PTH) were analysed.\textsuperscript{41} A greater incidence of hypophosphataemia was found following FCM (45.5% versus 4%), with severe and life-threatening hypophosphataemia only resulting after infusion of FCM (\(<0.6\) and \(<0.3 \text{ mmol/L}\)). The median duration of hypophosphataemia was 41 days; however, in 13 cases, this lasted for more than 2 months.\textsuperscript{41} An analysis of the impact of different preparations on bone markers could not take place due to the small numbers of paired samples in the FDI group. Baseline phosphate and choice of i.v. iron preparation (FCM versus FDI: OR 20.8, 95% CI 2.6–166; \(p<0.05\)) were the only independent predictors of development of hypophosphataemia.\textsuperscript{41} Other RCTs and observational studies have studied the association between third-generation i.v. iron preparations and hypophosphataemia, and some have provided evidence on the potential underlying mechanisms (Table 2).\textsuperscript{15,30,35–85} Large-scale RCTs such as FERWON-Nephro (CKD-specific) and FERWON-IDA (general IDA) (combined \(n=3050\)) have included the incidence of hypophosphataemia as a prespecified endpoint and compared FDI with iron sucrose; no incidence of severe hypophosphataemia (\(<0.3 \text{ mmol/L}\)) was seen.\textsuperscript{15,67} Conversely, in a number of RCTs and observational studies, FCM administration has been associated with the incidence of hypophosphataemia in 2.5–87% of participants. Severe hypophosphataemia, where reported, ranged between 0.0–11.3% in RCTs and 3.0–29.1% in observational studies. Real-world evidence on the use of FCM in patients with IBD has also suggested that moderate-to-severe hypophosphataemia following FCM infusion is associated with a significantly prolonged hospital stay when compared to patients where no or mild hypophosphataemia is experienced (mean (SD): 18 (19.8) versus 10.9 (13.4); \(p=0.0035\)).\textsuperscript{80} The impact of FCM on FGF23 appears to be dependent on the underlying cause of IDA. A prospective, single-centre observational cohort study (control: 20, pregnant: 20, CKD: 25) monitored the effect of a single infusion of 1000 mg FCM on bone metabolism markers.\textsuperscript{73} In all groups, iFGF23 was significantly elevated after FCM administration, returning to baseline levels by day 21 in the pregnant and CKD groups but remaining high in the control group (day 42). In all cases, cFGF23 was reduced. Moreover, FEPi % increased significantly across all groups (\(p<0.001\)), returning to baseline by day 21 in pregnant and CKD individuals but taking longer in the control group, potentially reflecting the persistent rise in iFGF23. The normalization of any change to phosphate took longer in the control and CKD groups. Calcitriol was significantly decreased in all groups until day 7 and remained significantly affected until day 21 in the control group. A multivariate analysis identifying the potential causes for hypophosphataemia reported that baseline phosphate concentration, dose of FCM, and phosphate excretion were significant predictors. No patients with CKD reported hypophosphataemia during the study, and this could be related to the baseline phosphate of these patients and...
Table 2. Comparative results of hypophosphataemia in RCTs and observational studies including third-generation i.v. irons.

| Study | Design | Population | Participants randomized | Comparators | Dosing | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/phosphate studies |
|-------|--------|------------|-------------------------|-------------|--------|----------|-------------------------------|---------------------------------------|-------------------------------------|
| Bailie et al. | RCT – crossover | IDA | 559 | FCM versus placebo | Single infusion: 15 mg/kg, maximum 1000 mg | 14 days | Not defined | 16.1% | No |
| Evstatiev et al. | RCT | IBD | FCM: 244; IS: 239 | FCM versus IS | FCM: 3 × 1000 or 500 mg; IS: 11 × 200 mg (Ganzoni based) | 12 weeks | Not defined | FCM: 2.5%; IS: 15.0% p=0.03 | No |
| Barish et al. | RCT | IDA | FCM: 709; SMC: 726 | FCM versus SMC | Multiple dose (FCM 15 mg/kg up to a single dose of 750 mg at 100 mg per minute weekly until the calculated iron deficit dose had been administered to a maximum cumulative dose of 2250 mg) and single dose (750 mg FCM or 15 mg/kg, whichever was smaller) | Multidose: 42 days; single dose: 30 days | Serum phosphate <0.64 mmol/L | Serum phosphate (FCM: 7.0%; SMC: 0.0%, p=0.001) | No |
| Charytan et al. | RCT | CKD (HD and NDD-CKD) | FCM: 254; SMC: 259 | FCM versus oral iron versus no iron | 15 mg/kg to a maximum of 1000 mg i.v.; if on HD (50 patients), received 200 mg bolus | 30 days | Not defined | FCM: 4.3%; SMC: 1% | No |
| Hussain et al. | RCT | IDA | FCM: 82; ID: 78 | FCM versus ID | Single maximum dose (15 mg/kg body weight up to 750 mg) administered weekly until the total iron requirement (calculated by the Ganzoni formula) or a maximum of 2250 mg was reached | 7 weeks | Serum phosphate <0.64 mmol/L | Serum phosphate (FCM: 8.5%; ID: 0%; p=0.05) | Greater mean decrease of phosphate from baseline to final value (p=0.001) with FCM |
| Wolf et al. | RCT | Female IDA | FCM: 25; ID: 30 | FCM versus ID | Single dose 15 mg/kg or up to 1000 mg | 35 days | Serum phosphate <0.64 mmol/L | Serum phosphate (FCM: 58.8%; ID: 0%) | FOM: iFGF23 significantly raised on days 1 and 7 from baseline (p=0.05); significant concomitant fall of calcitriol with FOM on days 1 and 7; non-significant trend for PTH increase this was not exhibited with ID |
| Reinisch et al. | RCT | IBD | FDI: 225; oral: 113 | FDI versus oral iron | FDI: according to Ganzoni formula | 8 weeks | Serum phosphate <0.64 mmol/L | Serum phosphate (FDI: week 2: 7%; week 8: 1%; oral iron: week 2: 1%, week 8: 1%) | No |
| Favrat et al. | RCT | Female ID/IDA | FCM: 144; placebo: 146 | FCM versus placebo | FCM: 1000 mg | 56 days | Serum phosphate <0.80 mmol/L | 86% (by day 7) | Resolved spontaneously in the majority of patients by the end of the study - 91.9% |

(Continued)
| Study           | Design | Population                   | Participants randomized | Comparators                  | Dosing                           | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/ phosphate studies |
|----------------|--------|------------------------------|-------------------------|------------------------------|---------------------------------|----------|------------------------------|--------------------------------------|---------------------------------------|
| Onken et al.   | RCT    | IDA                          | FCM: 503; oral iron: 257; SMC: 251 | FCM versus oral iron versus SMC | FCM: 2 × 750 mg                | 35 days  | Not defined                  | FCM: 46.7%                            | No                                    |
| Onken et al.   | RCT    | NDD-CKD                      | FCM: 1276; IS: 1285     | FCM versus IS                | FCM: 2 × 750 mg; IS: 5 × 200 mg (max) | 56 days  | Not defined                  | FCM: 18.5%; IS: 0.8%                   | No                                    |
| Macdougall et al. | RCT | NDD-CKD                      | FCM: 305; oral iron:308 | FCM versus oral iron         | FCM: targeting high ferritin or low ferritin; FCM high ferritin: initial single dose: 1000 mg (or 500 mg × 2 weight dependent), FCM low ferritin: 200 mg; i.v. if ferritin <100 µg/L during weeks 4–48; FCM high ferritin: every 4 weeks 500 mg iron if ferritin was in the range 200–<400 µg/L, or 1000 mg iron if ferritin was <200 µg/L; FCM low ferritin: every 4 weeks, 200 mg if ferritin was <100 µg/L | 52 weeks | Not defined                  | Nil stated                             | Drop in phosphate noted at 14, 8, 12, 24, 36, and 52 weeks with FCM |
| Johansson et al. | RCT | Cardiac surgery (non-anaemic) | FDI: 30 placebo: 30     | FDI versus placebo            | FDI: 1000 mg                    | 4 weeks  | Serum phosphate <0.64 mmol/L | Nil identified                        | No                                    |
| Bhandari et al. | RCT | HD-CKD                       | FDI: 234; IS: 117       | FDI versus IS                | FDI: either single 500 mg bolus or 500 mg split; IS: 500 mg split | 8 weeks  | Serum phosphate <0.64 mmol/L | FDI: 1.3%; IS: 2.6%                    | No                                    |
| Mahey et al.   | RCT    | Female IDA                   | FDI: 30; IS: 30         | FCM versus IS                | Ganzoni formula                 | 12 weeks | Not defined                  | FCM: 50.0%; IS: 40.0%                  | No                                    |
| Birgegård et al. | RCT | Non-myeloid cancer          | FDI: 231; oral iron:119 | FDI versus oral iron         | Ganzoni formula; either as twice max per week (1000 mg each time, infusion) or once per week (500 mg, bolus) | Serum phosphate <0.64 mmol/L | FDI: 7.9%; oral iron: 5.4% | No                                    |
| Kalra et al.   | RCT    | NDD-CKD                      | FDI: 233; oral iron:118 | FDI versus oral iron         | Ganzoni formula; either 1000 mg infusion or 500 mg bolus until replete | Serum phosphate <0.64 mmol/L | FDI: 1.7%; oral: 0.9%               | No                                    |
| Dahlerup et al. | RCT | IBD                          | FDI: 21                 | FDI                           | 1500 mg: 7 patients; 2000 mg: 8 patients; 2500 mg: 4 patients; 3000 mg: 2 patients | Serum phosphate <0.64 mmol/L | FDI: 9.5%                          | No severe hypophosphataemia reported; iFGF23 measured: no overt or significant changes stated | (Continued) |
| Study          | Design | Population                        | Participants randomized | Comparators | Dosing                  | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/ phosphate studies                                                                 |
|---------------|--------|-----------------------------------|-------------------------|-------------|-------------------------|----------|-----------------------------|--------------------------------------|----------------------------------------------------------------------------------|
| Roberts et al. | RCT    | HD-CKD                            | FCM: 22; IS: 20         | FCM versus IS | FCM: 200 mg; IS: 200 mg | 42 days  | Not defined                | No hypophosphataemic events noted                                            | Phosphate decreased significantly between D0 and D2 following FCM (p = 0.03); iFGF23 decreased significantly (p < 0.005) and cFGF23 increased significantly (p = 0.04); no changes with IS |
| Seid et al.   | RCT    | Female IDA (mixed postpartum and menorrhagia) | FCM: 9.96; SMC: 102    | FCM versus SMC | FCM: 15 mg/kg (max 1000 mg) single dose | 30 days  | Not defined                | FCM: 0.6%; SMC: 0.0%                                                             | Greater proportion of patients had a drop in phosphate with FCM (0.9% versus 0%; p < 0.001) |
| Breymann et al. | RCT   | Pregnant                          | FCM: 126; oral iron: 126 | FCM versus oral iron | FCM: 1000–1500 mg                | 12 weeks | Serum phosphate <0.64 mmol/L | FCM: 8.1%; oral iron: 0.8%                                                  | No                                                                                   |
| Derman et al. | RCT    | IDA                               | FDI: 34; IS: 169        | FDI versus IS | FDI: body weight and then either as infusion of 1000 mg or 500 mg bolus until repleted; IS: Ganzoni formula with repeated 200 mg infusions | 5 weeks  | Not defined                | FDI: 1.5%; IS: 0%                                                             | No                                                                                   |
| Holm et al.   | RCT    | PPH                               | FDI: 97; oral iron: 99  | FDI versus oral iron | FDI: 1200 mg                   | 12 weeks | Serum phosphate <0.64 mmol/L | FDI: 5.2%; oral iron: 2.0%                                                   | No                                                                                   |
| Shim et al.   | RCT    | Pregnancy                         | FCM: 46; oral iron: 44  | FCM versus oral iron | FCM: 1500 mg                  | 12 weeks | Not defined                | 0% in either arm                                                            | No                                                                                   |
| Adkinson et al. | RCT   | IDA                              | FCM: 1000; ferumoxytol: 997 | FCM versus ferumoxytol | FCM: 2 × 750 mg; ferumoxytol: 2 × 510 mg | 5 weeks  | Serum phosphate <0.64 mmol/L | FCM: 3.87%; ferumoxytol: 0.4%                                               | Statistical significance in phosphate between FCM and ferumoxytol at day 8, week 2, and week 5 (p < 0.001) and FEP (%) (FCM > ferumoxytol) at day 8, week 2 (p < 0.001), and week 5 (p < 0.05); results further explored through nested analysis by Wolf et al. |
| Gybel-Brask et al. | RCT  | Female blood donors             | FDI: 43; placebo: 42    | FDI versus placebo   | FDI: 1000 mg                  | 24 weeks | Serum phosphate <0.64 mmol/L | FDI: 2.4%                                                              | No                                                                                   | 

(Continued)
Table 2. (Continued)

| Study        | Design | Population | Participants randomized | Comparators | Dosing | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/ phosphate studies |
|--------------|--------|------------|-------------------------|-------------|--------|----------|-------------------------------|--------------------------------------|--------------------------------------|
| Wolf et al.  | RCT – sub-analysis of Adkinson et al. | IDA | FCM: 98; ferumoxytol: 87 | FCM versus ferumoxytol | FCM: 2 × 750 mg; ferumoxytol: 2 × 510 mg | 5 weeks | Serum phosphate <0.67 mmol/L | FCM: 5.8%; ferumoxytol: 0.9%; p < 0.001 | FEPi %; mean difference between FCM and ferumoxytol week 2 (FCM > ferumoxytol): 7.3% (95% CI 2.3–12.3); p = 0.004; calcitriol: % change in patient values from baseline to week 2: FCM: –60.4 ± 25.9%; ferumoxytol: –2.5 ± 28.0%; p < 0.001; iFGF23 % change in patient values from baseline to week 2: FCM: +302.8 ± 326.2%; ferumoxytol: +10.1 ± 61.0%; p < 0.001; cFGF23 % change in patient values from baseline to week 2: FCM: +119 ± 124.7; ferumoxytol: –41.5 ± 57.6%; p < 0.001; PTH % change in patient values from baseline to week 2: FCM: +18.5%; IS 20.2% |
| Drexler et al. | RCT | Blood donors | FCM: 86; oral iron: 90 | FCM versus oral iron | FCM: 1000 mg | 84 days | Serum phosphate <0.84 mmol/L | FCM: 17.4% | No |
| Jose et al.  | RCT | Pregnant | FCM: 50; IS: 50 | FCM versus IS | As per Ganzoni formula (maximal 1000 mg for FCM) | 12 weeks | Not defined | FCM: 4.0%; IS: 6.0% | No |
| Ikuta et al. | RCT | Female IDA | FCM: 119; IS: 119 | FCM versus IS | Patients allocated on 1000 mg or 1500 mg; where 1000 mg allocated: mean cumulative dose: FCM: 988.2 mg; IS: 910.0 mg; where 1500 mg allocated: FCM: 1485.2 mg; IS: 1414.0 mg | 12 weeks | Not defined | Not reported | Stated phosphate decrease: FCM 18.5%; IS 20.2% |
| Auerbach et al. | RCT | IDA | FDI: 989; IS: 494 | FDI versus IS | FDI: 1000 mg single dose; IS: 200 mg up to 5 times | 8 weeks | Serum phosphate <0.64 mmol/L | FDI: 3.9%; IS: 2.3% | No |
Table 2. (Continued)

| Study          | Design | Population | Participants randomized | Comparators | Dosing | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/ phosphate studies                                                                 |
|----------------|--------|------------|-------------------------|-------------|--------|----------|-------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------|
| Wolf et al.36  | RCT    | IDA        | FCM: 122; FDI: 123      | FCM versus FDI | FCM: 750 mg x 2; FDI: 1000 mg | 35 days  | Serum phosphate <0.64 mmol/L | FCM: 74.4%; FDI: 8.0% (p<0.001)          | Severe hypophosphataemia (<0.32 mmol/L) incidence: FCM: 11.3%; FDI: 0.0%; significant difference between hypophosphataemia incidence at all timepoints (p<0.001); FCM caused a significant increase in iFGF23 compared to the decrease caused by FDI (p<0.001 at all timepoints) and a considerably less decrease in cFGF23 compared to FDI (p<0.001) until day 35; FEP % was increased after FCM infusion and there was a considerable difference in the mean change between the two groups following infusion until day 21 (p<0.01); PTH also increased following FCM, while unaffected by FDI and the difference between the groups was significant at days 14-35 (p<0.001); calcitriol decreased following the infusion of both i.v. preparations; there was a significantly greater decrease following FCM than FDI at all timepoints (p<0.001) |

(Continued)
| Study            | Design | Population | Participants randomized | Comparators | Dosing                                      | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/ phosphate studies |
|------------------|--------|------------|-------------------------|-------------|--------------------------------------------|----------|-------------------------------|--------------------------------------|--------------------------------------|
| Emrich et al.    | RCT    | Female IDA | FCM: 13; FDI: 13        | FCM versus FDI | Single infusion: 20 mg/kg body weight (maximum: 1000 mg) | 37 days  | Serum phosphate <0.64 mmol/L | FCM: 7.9%; FDI: 8%; p=0.001          |                                      |
|                   |        |            |                         |             |                                             |          |                               |                                      | if iFGF23; significant rise with FCM (p<0.001) but no change with FDI (p=0.140); there was a significant difference between the two variables on day 1 post infusion (p<0.001); cFGF23: decrease in serum cFGF23 with both infusions (p>0.120, respectively); there was a significant difference between the two groups on day 1 highly driven by the significant decrease in cFGF23 following FDI infusion (p<0.05); calcitriol was significantly affected by either infusion, with a noticeable decrease following FCM (p=0.001); there was a significant difference between the two treatments on days 1 and 7 following i.v. iron infusion driven by the decrease in calcitriol due to FCM (p<0.001 and p=0.002, respectively) |
| Bhandari et al.  | RCT    | NDD-CKD    | FDI: 1027; IS: 511      | FDI versus IS | FDI: 1000 mg single dose; IS: 200 mg up to 5 times | 10 weeks | Serum phosphate <0.64 mmol/L | FDI: 3.2%; IS: 0.38%; p=0.004        | Severe hypophosphataemia <0.32 mmol/L: 0.00% in both groups |
|                   |        |            |                         |             |                                             |          |                               |                                      |                                      |
| Malone et al.    | Pooled analysis (from 5 RCTs) | IDA (bariatric surgery) | FCM: 123; SMC: 126 | FCM versus SMC | NA                                         | NA       | Not defined in manuscript | FCM: 4.9%; SMC: p=0.05                | No                                    |

(Continued)
| Study          | Design       | Population          | Participants randomized | Comparators | Dosing                                                                 | Duration | Hypophosphataemia definition                                                                 | Reported hypophosphataemia incidence | Other bone markers/phosphate studies |
|----------------|--------------|---------------------|-------------------------|-------------|------------------------------------------------------------------------|----------|-----------------------------------------------------------------------------------------------|--------------------------------------|-------------------------------------|
| Hardy et al.   | Observational| ID/IDA              | FCM: 78; IS: 52         | FCM versus IS | FCM: mean dose: 2123 mg (quartile: 1000–2000 mg); IS: mean dose 701 mg (quartile 200–800) | NA       | Moderate: 0.32–0.64 mmol/L                                                                   | FCM: 51%; IS: 22%                     | Severe: <0.32 mmol/L; 13%; FCM dose was associated with hypophosphataemia; mean hypophosphataemia duration was 6 months (2–9 months); 30% of patients with FCM-induced hypophosphataemia complained about fatigue worsening |
| Schaefer et al.| Observational | Gastroenterology    | FCM: 55; FDI: 26        | FCM versus FDI | Dosage was divided into 500 mg, 1g and >1g                             | NA       | <0.8 mmol/L; severe: <0.6 mmol/L; life-threatening: <0.3 mmol/L                              | FCM: 45.5%; FDI: 3.9%                 | Severe and life-threatening only with FCM: 29.1% and 3.6%, respectively |
| Toledano et al.| Observational | Haematological and solid tumours | 367                     | FCM         | Median dose: 1000 mg                                                   | NA       | Not defined                                                                      |                                      |                                     |
| Bager et al.   | Observational | Gastroenterology    | 231 patients: FCM: 192 infusions; FDI: 116 infusions; 39 patients received both types | FCM versus FDI | Median dose: 1000 mg                                                   | 10 weeks | Serum phosphate <0.64 mmol/L and serum phosphate <0.32 mmol/L                     |                                      | Greater phosphate drop (>50%) following FCM than FDI at weeks 2 and 5 (p<0.001) |
| Sari et al.    | Observational | Kidney transplant   | 23 patients (+2 index cases) | FCM         | Single dose; mean dose: 896 mg (median: 1000 mg)                      | NA       | Not defined in manuscript but defined severe hypophosphataemia as <0.50 mmol/L        | 56.5%; severe in 34.8%               | Median time to hypophosphataemia: 15 days (3–24); median duration of hypophosphataemia: 41 days (2–99) |

(Continued)
Table 2. (Continued)

| Study        | Design   | Population                  | Participants randomized | Comparators | Dosing          | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/ phosphate studies                                                                 |
|--------------|----------|-----------------------------|-------------------------|-------------|-----------------|----------|------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------|
| Stohr et al. | Observational | Cardiology – heart failure | 23 patients            | FCM         | Single dose: 1000 mg | 28 days  | Serum phosphate <0.80 mmol/L | 60.9%                                | Divided patients into CKD (12) and non-CKD (11) according to eGFR (<60 ml/min/1.73 m<sup>2</sup>): more evident hypophosphataemia in those with no CKD; additionally, a >50% decrease in calcitriol was noted in both groups following infusion of FCM; iFGF23 increased in both populations (during first 7 days) while cFGF23 decreased (until day 14) and then started normalizing with no complete return to baseline by day 28 |
| Huang et al. | Observational | Female IDA + CKD + control | 65 (control 20; pregnant 20; CKD 25) | FCM         | Single dose: 1000 mg | 42 days  | Not defined                  | Not reported                         | iFGF23 increased irrespective of group: CKD and pregnant group: normalized by day 21; control group normalized by day 42; iFGF23 to cFGF23 ratio: increased significantly by day 2; persisted to day 21 in control group and day 42 in pregnant and CKD groups; FEP %: increased significantly for all groups; returned to baseline by day 32 in pregnant and CKD groups but remained significantly elevated in control group at day 42 |
| Hofman et al. | Observational | HD-CKD                      | 221 (switched from IS to FCM) | FCM versus IS | Weekly dose: FDI: 48 mg/ week versus IS: 55 mg/week; p<0.04 | 15 months | Not defined                  | Not reported                         | A non-significant drop in phosphate (0.03 mmol/L) was noted |
### Table 2. (Continued)

| Study                  | Design   | Population      | Participants randomized | Comparators  | Dosing                        | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/ phosphate studies |
|------------------------|----------|-----------------|--------------------------|--------------|-------------------------------|----------|------------------------------|---------------------------------------|--------------------------------------|
| Detlie et al.          | Observational | IBD             | FCM: 52; FDI: 54         | FCM versus FDI | Single dose: 1000 mg          | 6 weeks  | Serum phosphate <0.80 mmol/L | At week 2: FCM: 7.2%, FDI: 11.3% (p<0.001) | Moderate-to-severe hypophosphataemia (<0.65 mmol/L): at week 2: FCM: 56.9%, FDI: 5.7%; p<0.001 |
|                        |          |                 |                          |              |                               |          |                              | At week 6: FCM: 21.6%, FDI: 3.7% (p=0.0013) | At week 6: FCM: 13.7%, FDI: 1.9%; p=0.054 |
|                        |          |                 |                          |              |                               |          |                              | Severe hypophosphataemia throughout study: FCM: 1.92%; FDI: 0.0%; no differences noted with regards to 25-hydroxyvitamin D and ALP |
| Sivakumar et al.       | Observational | NDD-CXG        | FDI: 708; ID: 783        | FDI versus LMWID | Dose range: FDI: 1000–1500 mg; ID: 750–1500 mg | 182 days | Not defined                  | Not reported                          | Levels of phosphate were not significantly affected after administration of iron |
| Ikuta et al.           | Observational | IDA (gastro)  | 500 mg per dose; dosage requirement: 1000 mg: Hb level 10 g/dL + body weight <70 kg; 1500 mg: all other patients received iron | 12 weeks | Serum phosphate <0.81 mmol/L | 92.10%   | Severe hypophosphataemia <0.32 mmol/L: 5.13% |
| Ding et al.            | Observational | IDA             | 24                       | FCM          | Escalation study: 12 participants: 500 mg; 12 participants: 1000 mg | Not stated | Serum phosphate <0.80 mmol/L | 75%                                   | Low-dose cohort: 58.3%, high-dose cohort 91.7%; one episode of severe hypophosphataemia in high-dose cohort (8.3%) |
| Abdel-Razeq et al.     | Observational | Oncology (chemotherapy) | 84                       | FCM          | 1000–2000 mg (single dose up to 1000 mg with subsequent dose as need) | 12 weeks | Serum phosphate <0.64 mmol/L | 46.4%                                 | All patients reported asymptomatic three groups dependent on iron deficiency status (other/functional/absolute) – greatest incidence of hypophosphataemia in patients with absolute as opposed to functional IDA (65.4% versus 25.0%; p=0.04) |

(Continued)
| Study                  | Design                                      | Population     | Participants randomized | Comparators | Dosing                   | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/phosphate studies |
|-----------------------|---------------------------------------------|----------------|-------------------------|-------------|--------------------------|----------|------------------------------|--------------------------------------|-------------------------------------|
| Jesus-Silva et al.    | Observational – real-world data HD-CKD     | 190 patients   | (doses: FDI: 41,295 prescriptions; IS: 14,685 doses) | FDI versus IS | NA                       | 12 months | Not defined                 | No events                             | No                                  |
| Fragkos et al.        | Observational – real-world data IDA         | 162 patients   |                         | FCM         | Median dose: 1000 mg     | 90 days  | Serum phosphate <0.80 mmol/L | 87%                                  | Mild hypophosphataemia: 0.3%; moderate hypophosphataemia (<0.65 mmol/L): 33.7%; severe hypophosphataemia (<0.32 mmol/L): 3.0% |
| Fang et al.           | Observational  IBD and control              | 44 (IBD: 24; control: 20) |                         | FCM         | 1000 mg                  | 28 days  | Serum phosphate <0.80 mmol/L | At 28 days: 72.7% Mild hypophosphataemia (<0.60 mmol/L): 55%; serum iFGF23 mean rise: 84% (95% CI 26–139); p=0.004, peaking at day 2 and normalizing by day 28; serum cFGF23: continued declining with significant reduction by day 28 (p=0.004, paired t-test) |
| Frazier et al.        | Observational Female IDA                    | 16             |                         | FCM         | 750 mg × 2               | 5 weeks  | Serum phosphate <0.81 mmol/L | 87.50% Severe hypophosphataemia (<0.32 mmol/L): 25%; iFGF23: significant increase to week 2: +134.0% (40.6–305.8); p<0.001 and remained significantly higher by week 5: +16.4 pg/mL (-0.4 to 45.8); p=0.014; cFGF23: significant decrease to week 2: -310.1 RU/mL (-750.8 to -116.3); p=0.002 and remained significantly lower by week 5: -324.6 RU/mL (-763.3 to 123.2), p<0.001 |
### Table 2. (Continued)

| Study            | Design   | Population            | Participants randomized | Comparators | Dosing                  | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/ phosphate studies                  |
|------------------|----------|-----------------------|-------------------------|-------------|-------------------------|----------|-------------------------------|---------------------------------------|-------------------------------------------------------|
| Frazier et al.   | Observational | Bariatric patients | 52                      | FCM         | Single dose: 500 or 1000 mg (Median: 500 mg) | 12 weeks | Serum phosphate <0.80 mmol/L | 29%                                   | Moderate-to-severe hypophosphataemia (<0.60 mmol/L):21%; phosphate values normalized in all patients within 49 days; FEP % increased from 6.7% (4.1%–10.5%) to 12.2% (7.7%–18.2%; p<0.001); iFGF23 increased significantly by 30% (−3.8% to 90.0%); p=0.001; cFGF23 significantly decreased by 19.1% (−40.8% to 15.5%; p=0.018); calcitriol significantly decreased from 64 ng/L (51-81 ng/L) to 42 ng/L (30–52 ng/L); p<0.0001 |
| (Cont.)          |          |                       |                         |             |                         |          |                               |                                                       |                                                       |

- Frazier et al. (Cont.)

- Schoeb et al. (Cont.)
Table 2. (Continued)

| Study                | Design    | Population                  | Participants randomized | Comparators | Dosing                                          | Duration | Hypophosphataemia definition | Reported hypophosphataemia incidence | Other bone markers/phosphate studies |
|----------------------|-----------|-----------------------------|-------------------------|-------------|------------------------------------------------|----------|------------------------------|---------------------------------------|-------------------------------------|
| Dashwood et al. 84    | Observational | Cardiology – heart failure | 173                     | FCM         | Not specified: single dose <1000 mg             | 60 days  | Serum phosphate <0.64 mmol/L | 27%                                   | Classified as severe hypophosphataemia (0.4–<0.64 mmol/L): 44 patients (25%); extreme (<0.4 mmol/L): 3 patients (2%); identified reduced creatinine clearance as protective factor; median time to nadir 8 days (interquartile range: 4–16 days). |

ALP, alkaline phosphatase; cFGF23, cleaved FGF23; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FCM, ferric carboxymaltose; FDI, ferric desironaltose; FEPi %, fractional excretion of phosphate; FGF23, fibroblast growth factor 23; Hb, haemoglobin; HD-CKD, haemodialysis-dependent chronic kidney disease; IBD, inflammatory bowel disease; ID, iron deficiency; IDA, iron deficiency anaemia; iFGF23, intact FGF23; IS, iron sucrose; i.v., intravenous; LMWID, low-molecular-weight iron dextran; NA, not available; NDD-CKD, non-dialysis-dependent chronic kidney disease; PPH, postpartum haemorrhage; PTH, parathyroid hormone; RCT, randomized controlled trial; SMC, standard medical care.
phosphate handling in renal disease. Additionally, evidence from the FIND-CKD trial (n=626), where FCM (at different doses) and oral iron were compared, suggested that the magnitude of hypophosphataemia could be dose related (mean change in phosphate: FCM high dose: −0.17 mmol/L at 4 weeks, −0.13 mmol/L at 12 weeks; FCM low dose: −0.01 mmol/L at 4 weeks, +0.02 mmol/L at 12 weeks).

Given the garnered interest, disease-specific studies comparing third-generation i.v. iron and their impact on phosphate metabolism, such as PHOSPHARE-IBD (NCT03466983) and ExplorIRON-CKD (EudraCT: 2019-004370-26), are currently enrolling patients. As there is increasing awareness of the underlying mechanism, it is important to consider the clinical implications of FGF23 imbalance and hypophosphataemia.

**FGF23 – the implications**

FGF23 appears to be the key messenger in the manifestation of hypophosphataemia following i.v. iron administration. Murine experiments have previously indicated that iron deficiency stimulates both FGF23 transcription and degradation to the inactive cFGF23 form. As such, phosphate levels remain constant during IDA; however, for reasons not yet elucidated, FCM appears to reduce/inhibit the cleavage of iFGF23, causing a sequential rise in iFGF23 that leads to phosphate loss. Another possibility is that of secondary induction of hepatic or lymphatic ectopic production of FGF23 due to FCM without a parallel increase in cleavage, again leading to an increase in biologically active iFGF23. This potential elevation in iFGF23 may result in pathophysiological consequences with regard to bone and other organs that are affected in a paracrine fashion such as the heart.

This imbalance in FGF23 concentrations may lead to both acute and longer-term consequences due to effects on phosphate, reduction in calcitriol, and eventual increase in PTH (Figure 3). Osteomalacia has previously been reported as a result of long-term exposure to parenteral iron in conjunction to the probable effects of malnutrition and malabsorption in patients with IBD, where serum phosphate is persistently low and there is a possible associated vitamin D deficiency from poor intake and increased losses.

Intact FGF23 reduces calcitriol synthesis through transcriptional suppression of the enzyme 1α-hydroxylase that aids in the conversion of 25(OH) vitamin D to calcitriol. Calcitriol is a highly calcitropic active steroid hormone responsible for the effects of vitamin D. As calcitriol is indispensable for skeletal health and is associated with a reduction in cardiovascular disease, malignancy, and infection, it is possible that secondary vitamin D deficiency due to i.v. iron can lead to cardiovascular death, arterial stiffness, and endothelial dysfunction.

Another organ potentially affected through this imbalance is the heart. Epidemiological data have demonstrated that increased FGF23 concentrations are independently related to a greater risk of cardiovascular disease and death in patients with renal disease; however, causation has not been yet identified. The Chronic Renal Insufficiency Cohort and the Homocysteine in Kidney and End-Stage Renal Disease studies followed 4978 patients with CKD (not dialysis dependent on baseline) for an average of 3.5 years and 2.9 years, respectively. After adjustment for classical cardiovascular risk factors and for traditional markers of CKD-associated mineral bone disease, patient mortality was higher, more than two-fold in those with higher quartiles of baseline FGF23 compared to patients with the low baseline FGF23. Paul et al. demonstrated in cellular and murine experiments that FGF23 induces left ventricular hypertrophy (LVH) independent of klotho. They also reported that FGF receptor blockers could lead to an antagonism of the uraemia-induced LVH, and this was supplemented with serial echocardiographic studies among patients with CKD, in whom elevated FGF23 levels predicted the development of LVH. LVH predisposes to the development of left ventricular dysfunction and congestive heart failure, which may link experimental data on FGF23-induced myocardial hypertrophy with clinical evidence for a predictive role of FGF23 in incident heart failure. Post hoc analysis of heart failure therapies, such as angiotensin-conveting enzyme inhibitors, has also suggested an overall clinical benefit with decreasing FGF23 levels, but uncertainty still remains on the associations exhibited by these observational data.

FGF23 has also been evaluated both as a provoker and as a prognosticator in cardiovascular disease. Cohort studies have suggested that increased FGF23 levels are associated with recurrent coronary artery disease, incident coronary heart disease, and incident atrial fibrillation as well as with worse outcomes in heart failure; however, the strength of prognostication in heart failure has recently been challenged. Experimental theories nonetheless have highlighted the involvement of FGF23 in endothelial dysfunction, myocardial fibrosis, stimulation of, and co-operation with the renin–angiotensin–aldosterone system and LVH. Small-scale observational data have suggested that the use of FCM and the subsequent rise in iFGF23 does not have a detrimental effect on myocardial stress and damage, at least in the short term, as exhibited by no change in a number of cardiac markers. Other possible implications of FGF23 on cardiovascular dysfunction could potentially arise through biochemical pathways linked with sodium retention secondary to upregulation of the renin–angiotensin–aldosterone system via increased gene expression and change in calcium signalling.

**Hypophosphataemia – the clinical implications**

Hypophosphataemia is common in hospitalized patients with sepsis or those requiring intensive care therapy for critical illness. Additionally, it is prevalent in populations where malnutrition or malabsorption exists. Evidence also suggests an increasing incidence of hypophosphataemia in the elderly and in association with a number of medications (Table 3). Hypophosphataemia severity can be graded based on laboratory values with values of 0.6–0.8 mmol/L representing mild, 0.3–0.59 mmol/L moderate, and <0.3 mmol/L
ACUTE HYPOPHOSPHATAEMIA can affect multiple organs, including the muscles and haematopoietic centres. Diaphragmatic contractility is severely affected and so is the myocardium, with reports suggestive of hypophosphataemia-induced respiratory failure, cardiomyopathy, and arrhythmias.\textsuperscript{114–119} It is hence not surprising that hypophosphataemia is a negative outcome predictor in patients admitted in intensive care units as it can lead to respiratory failure, necessary prolonged weaning time from ventilation, and increased length of stay.\textsuperscript{116,119} Moreover, hypophosphataemia is linked with fatigue, tremors, malaise, generalized weakness, neuropathy, irritability, and convulsions, and these non-specific symptoms can be mistaken as being associated with those symptoms commonly experienced with IDA.\textsuperscript{120} Rare cases of clinical presentations mimicking Guillain–Barre syndrome have also been reported to be associated with acute hypophosphataemia.\textsuperscript{21,121}

Figure 3. FGF23 stimuli, direct effects and impact on disease processes.

Fibroblast growth factor 23 (FGF23) can arise due to hyperphosphataemia, hyperparathyroidism, inflammation, hypoxia, chronic kidney disease, and iron deficiency. It is important to highlight that stimuli such as hyperparathyroidism increase both the production and cleavage of FGF23 and, therefore, the total effect may be neutral. The primary target of FGF23 is the decrease in phosphate concentration through complementary actions with klotho in the kidneys. It also causes the direct inhibition of secretion of parathyroid hormone. This effect is transient as the FGF23-driven suppression of calcium potentially restimulates parathyroid hormone production. However, FGF23 appears to also be linked in a variety of other disease processes, either as a prognosticator, a provoker, or a by-product, with a number of possible theories currently being investigated. Dashed lines represent the interconnections between disease states and biomarkers that can affect FGF23. AF, Atrial fibrillation; CKD, chronic kidney disease; IDA, iron-deficiency anaemia; LVH, left ventricular hypertrophy; PTH, parathyroid hormone.
monitoring a patient’s phosphate levels post infusion if symptoms persist or if new ones arise would be advisable. Patient education is paramount, and individuals should be made aware that symptoms of hypophosphataemia can be easily misdiagnosed as iron deficiency and, therefore, if symptoms persist or new symptoms arise, these should be appropriately investigated. Where post-administration hypophosphataemia is a possibility (e.g. vitamin D deficiency, secondary hyperparathyroidism), the clinician should consider the use of a preparation less likely to cause it or aggravate it. If an alternative is not available, dose adjustment should take place (i.e. decreased dose); however, hypophosphataemia can occur even following the administration of lower doses, and therefore, vigilance is needed. In cases where patients require long-term i.v. iron administration (e.g. IBD, CKD), osteomalacia assessment is required, especially if a preparation known to potentially cause hypophosphataemia is used. In these cases, and where multiple high doses are administered, regular monitoring of phosphate is advisable, and ideally, the prescription of an alternative preparation is advised. Monitoring should include vitamin D, PTH, and other blood investigations associated with phosphate metabolism. One should consider reviewing for acute effects of hypophosphataemia 2 weeks following infusion; if a downward trend is identified, consider repeating such investigations at the 5-week interval. It is important to acknowledge the recent change in the Food and Drug Administration drug label for FCM highlighting the causal relationship between FCM and hypophosphataemic osteomalacia and the need to monitor phosphate in patients receiving multiple high-dose infusions over a long-term treatment and those with risk factors (Table 4). If hypophosphataemia emerges following administration of iron, treatment should be guided based on severity and symptomatology, and we would suggest that no further iron is administered until hypophosphataemia resolves.

Chronic hypophosphataemia in adults affects the skeleton, leading to osteomalacia, muscle weakness, and eventual sarcopenia. In children, rickets and growth retardation occur. Mobility issues and fractures are common. Chronic hypophosphataemia can also affect the teeth, especially in cases of X-linked hypophosphataemia, where periodontitis is common.

### Approach to the patient, investigations and treatment options for hypophosphataemia

Prior to initiation of i.v. iron therapy, it would be prudent to assess the patient’s biochemical profile (including phosphate and vitamin D concentrations) alongside their underlying medical condition and the possibility of hypophosphataemia arising (Figure 4). It is also important to explain to the patient the link between hypophosphataemia and certain compounds and the symptoms to monitor. If hypophosphataemia is identified, it would be advisable for FCM to be avoided. Additionally,

| Table 3. Medications associated with hypophosphataemia. |
|----------------------------------------------------------|
| • Adrenaline                                               |
| • Dopamine                                                |
| • Salbutamol                                              |
| • Insulin                                                 |
| • Erythropoiesis-stimulating agents                       |
| • 6-mercaptopurine                                        |
| • Phosphate-binding antacids                              |
| • Protease inhibitors                                     |
| • Isoniazid                                               |
| • Rifampicin                                              |
| • Granulocyte macrophage – colony-stimulating factors     |
| • Diuretics                                               |
| • Aminoglycosides                                         |
| • Tyrosine-kinase inhibitors                              |
| • mTOR inhibitors                                         |
| • Bisphosphonates                                         |
| • Paracetamol poisoning                                   |
| • Denosumab                                               |
| • Ibuprofen                                               |
| • Gadolinium                                              |
| • Valproic acid                                           |
| • Aciclovir                                               |
| • Carbamazepine                                          |
| • Phenytoin                                               |
| • Corticosteroids                                         |
| • Teriparatide                                            |
| • Niacin                                                  |
| • Intravenous iron                                        |

| Table 4. Risk factors for the development of hypophosphataemia following intravenous administration of ferric carboxymaltose. |
|--------------------------------------------------------------------------------------------------------------------------|
| • Low baseline phosphate                                                                                                    |
| • Vitamin D deficiency                                                                                                      |
| • Hyperparathyroidism                                                                                                        |
| • Renal transplant recipient (with acceptable transplant function)                                                          |
| • Bariatric surgery                                                                                                          |
| • Medications                                                                                                               |
| • Increased age                                                                                                             |
| • Malnourishment                                                                                                            |
| • Malabsorption                                                                                                             |
| • Lower serum ferritin                                                                                                       |
| • Severe iron deficiency anaemia                                                                                             |

In cases where patients require long-term i.v. iron administration (e.g. IBD, CKD), osteomalacia assessment is required, especially if a preparation known to potentially cause hypophosphataemia is used. In these cases, and where multiple high doses are administered, regular monitoring of phosphate is advisable, and ideally, the prescription of an alternative preparation is advised. Monitoring should include vitamin D, PTH, and other blood investigations associated with phosphate metabolism. One should consider reviewing for acute effects of hypophosphataemia 2 weeks following infusion; if a downward trend is identified, consider repeating such investigations at the 5-week interval. It is important to acknowledge the recent change in the Food and Drug Administration drug label for FCM highlighting the causal relationship between FCM and hypophosphataemic osteomalacia and the need to monitor phosphate in patients receiving multiple high-dose infusions over a long-term treatment and those with risk factors (Table 4). If hypophosphataemia emerges following administration of iron, treatment should be guided based on severity and symptomatology, and we would suggest that no further iron is administered until hypophosphataemia resolves.
Once hypophosphataemia resolves, it would be appropriate to recommence treatment with a different i.v. iron preparation, taking into consideration the differences in dosing regimens that exist.

The treatment of hypophosphataemia depends on the pathophysiological background, chronicity, and symptoms. In the case of FGF23-associated hypophosphataemia as exhibited following i.v. administration of FCM, it would be reasonable to address the decrease in phosphate through direct supplementation of phosphate (oral/i.v.) with additional calcitriol provision in order to enhance calcium and phosphate reabsorption and decrease the stimulus for PTH.

We would strongly advise that symptomatic patients, those with severe hypophosphataemia and cases where oral phosphate administration is likely to not be tolerated or to fail due to impaired absorption, are treated with i.v. phosphate replenishment. Monoclonal antibody use has also shown promise both in vitro and in vivo, with cases reporting radiological resolution of osteomalacia and improvement of phosphate following the administration of burosumab in a patient developing hypophosphataemia and osteomalacia secondary to i.v. iron administration. Burosumab is a human anti-FGF23 monoclonal antibody approved for the treatment of X-linked hypophosphataemia in paediatric populations. Early studies indicated that burosumab increased serum phosphate through an increase in calcitriol and proximal tubular phosphate reabsorption. Rickets severity was reduced and an improved healing of fractures was noted alongside a decrease in stiffness.

**Conclusion**

Third-generation i.v. iron preparations are increasingly used as they are able to deliver large doses of iron safely without increasing hypersensitivity reactions. However, it is important to note that distinct safety profiles exist and these preparations are not interchangeable. Hypophosphataemia...
has emerged as an increasingly recognized adverse event following the administration of FCM secondary to changes in the metabolism of FGF23. Clinicians should be aware of this and develop an understanding of the short- and longer-term clinical impact and ways to address and minimize it. The appropriate management, monitoring, and review of potential hypophosphataemia and its associated causes (e.g. PTH, vitamin D) are key alongside personalized tailoring of prescription of i.v. iron to patients (considering the biochemical picture, background medical history, and concurrent medications) in order for i.v. iron to be administered safely. More studies are required to understand the patient-related impacts of i.v. iron-induced hypophosphataemia.

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