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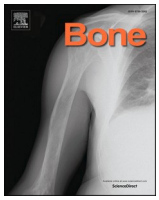

Review Article

Hypophosphatemia after intravenous iron therapy: Comprehensive review of clinical findings and recommendations for management

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ABSTRACT

Contemporary intravenous iron formulations allow administration of high doses of elemental iron and enable correction of total iron deficit in one or two infusions. An important but underappreciated complication of certain formulations is hypophosphatemia caused by increased secretion of the phosphaturic hormone, fibroblast growth factor 23 (FGF23). The pathophysiology of FGF23-induced hypophosphatemia due to certain intravenous iron formulations has been recently investigated in prospective clinical trials. To reach the correct diagnosis, clinicians must recognize the typical clinical manifestations of intravenous iron-induced hypophosphatemia and identify a specific pattern of biochemical changes (hyperphosphaturic hypophosphatemia triggered by high FGF23 that causes low 1,25 $(OH)_2$ vitamin D, hypocalcemia and secondary hyperparathyroidism). Physicians and patients should be aware of hypophosphatemia as a common complication of intravenous iron therapy and monitor serum phosphate concentrations in patients receiving repeated doses of specific intravenous iron formulations. Symptoms of hypophosphatemia are associated with severity and duration. Persistent hypophosphatemia can occur with iron therapy and can cause debilitating diseases including myopathy, osteomalacia and fractures. This review summarizes the current understanding of the iron-phosphate axis as well as complications of intravenous iron-induced hypophosphatemia.

1. Iron therapy and hypophosphatemia

Iron deficiency is common and affects >15% of the world population [1]. Poor gastrointestinal tolerability and limited uptake can render oral iron supplementation unfeasible or ineffective [2]. This has prompted the development of intravenous iron formulations, which are nanoparticles composed of iron(*III*)oxide-hydroxides and carbohydrates [3,4]. After intravenous infusion these complexes are removed from the circulation by uptake into macrophages, where nanoparticles are broken down and iron is slowly released mainly for delivery to the bone marrow [5]. The latest generation of iron formulations includes ferric carboxymaltose (FCM), ferric derisomaltose (FDI) (formerly known as iron isomaltoside) and ferrumoxytol. All three formulations allow rapid correction of total iron deficit in one or two infusions in the majority of patients, while exhibiting low rates of hypersensitivity reactions [6–8].

Despite their excellent short-term tolerability, hypophosphatemia has been reported in patients treated with FCM or FDI, and rarely after ferrumoxytol [9–11]. Systematic reviews and meta-analyses have recently shown that the incidence, severity and duration of hypophosphatemia is highest after FCM [12–14]. Pooled incidence of hypophosphatemia among patients included in 42 prospective clinical studies was 47% [95% CI 36–58%] in FCM treated patients as compared to 4% [95% CI 2–5%] in FDI treated patients [14,15]. A randomized clinical trial comparing hypophosphatemia incidence after two doses of 750 mg

Abbreviations: FCM, ferric carboxymaltose; FDI, ferric derisomaltose; FGF23, fibroblast growth factor 23; na, not available; TIO, tumor-induced osteomalacia.

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FCM with one dose of 1000 mg FDI showed that the overall incidence of hypophosphatemia was 8% after FDI and 74% in the FCM group. Only FCM was associated with severe hypophosphatemia (≤1 mg/dL) in 11% of patients, and hypophosphatemia was present in 45% of patients on the last study visit on day 35 [9]. While hypophosphatemia has previously been thought to be transient, it can persist for 6 months in about 5% of patients [14,16–18].

2. Mechanism of intravenous iron induced hypophosphatemia

Hypophosphatemia after FCM is associated with an increase in urinary phosphate excretion. This is mediated by the phosphaturic hormone fibroblast growth factor 23 (FGF23), which increases 3–6 fold beginning within the first day after FCM infusion. It is currently unknown why only FCM but neither FDI, iron dextran or ferrumoxytol, significantly increase FGF23. Differential effects on FGF23 could be in part attributed to differences in dose and administration schedules, but striking differences on FGF23 induction were also found after a single infusion of 1000 mg of FCM as compared to FDI or iron dextran [8,19,20]. Therefore, it is likely that the specific physico-chemical properties of FCM trigger increases in FGF23 [3,4]. In accord with the known physiological function of FGF23, this increase causes reduced proximal tubular absorption of phosphate from the glomerular filtrate and consequently increased urinary phosphate excretion [21]. Patients with impaired kidney function have a significantly lower risk of developing hypophosphatemia after FCM, because reduced glomerular filtration rate limits the filtered amount of phosphate and thus the amount that can be excreted in the urine [22]. The production of FGF23 is transcriptionally and post-translationally controlled [23]. The expression of the FGF23 gene is increased by inflammation and iron deficiency [24]. Accordingly, patients with iron deficiency have been found to exhibit a strong increase in biologically inactive proteolytic fragments of FGF23, which do not act as phosphaturic hormone [9,19]. Treatment with either of the intravenous iron formulations is associated

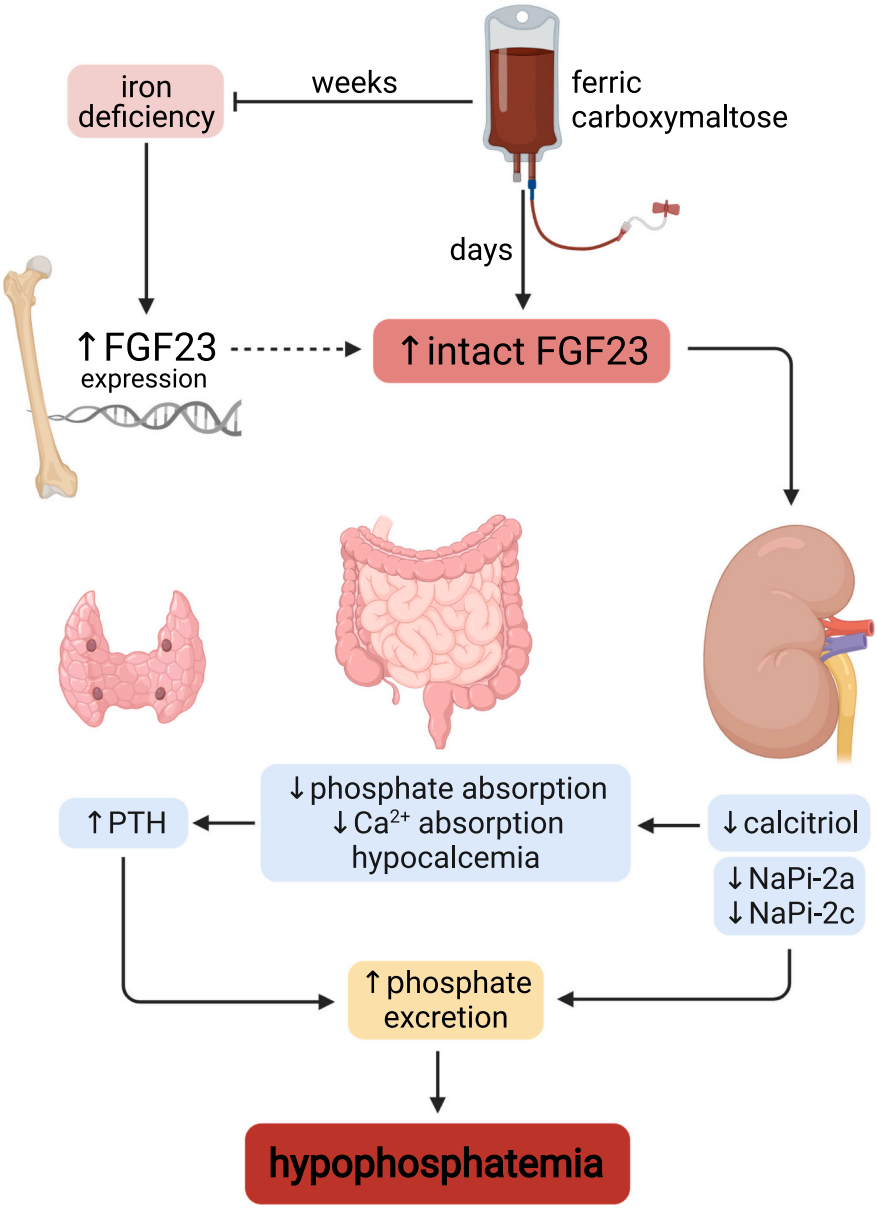

Fig. 1. Proposed mechanism of FCM-induced hypophosphatemia. Treatment with ferric carboxymaltose corrects iron deficiency within weeks but increases intact FGF23 within one day. The biochemical effects include increased urinary phosphate excretion, decreased calcitriol production, hypocalcemia and secondary hyperparathyroidism, which further increases urinary phosphate excretion. Created with BioRender.com.

with a rapid normalization of plasma concentrations of C-terminal FGF23 fragments within 24 h after infusion [9,19]. Post-translationally, FGF23 is controlled by limited proteolysis at a consensus serine protease recognition site, which is recognized by several prohormone convertases, but cleave FGF23 only when phosphorylated by the protein kinase 'Family with sequence similarity 20C' (FAM20C) [25]. In contrast, FGF23 is tagged for secretion as intact phosphaturic hormone when the peptide is O-glycosylated by the enzyme N-acetylgalactosaminetransferase 3 (Galnt3) [26]. High dietary phosphate exposure has been shown to increase the secretion of intact FGF23 mainly by increased glycosylation and subsequently decreased degradation [23]. Inhibition of FGF23 cleavage by intravenous iron has been proposed to cause intravenous iron-induced hypophosphatemia [19,21].

Besides its effects as a phosphaturic hormone, FGF23 also inhibits the activation of 25 (OH) vitamin D to 1,25 $(OH)_2$ vitamin D (calcitriol). At the same time further metabolism to 24,25 $(OH)_2$ vitamin D is increased by FGF23. The decrease in calcitriol leads to mild hypocalcemia, which subsequently causes an increase in circulating parathyroid hormone (PTH) concentration. While the increase in PTH protects against severe hypocalcemia in the setting of reduced calcitriol levels, the phosphaturic effects of PTH further prolong hypophosphatemia beyond the period of FGF23 elevation (Figs. 1 and 2) [19,27].

This sequence of biochemical changes can affect. bone metabolism and ultimately result in osteomalacia. The main mechanism of intravenous iron-induced hypophosphatemia is mediated by high FGF23 and increased urinary phosphate excretion. As explained, secondary hyperparathyroidism can not only aggravate hypophosphatemia but also directly increases bone turnover. Data from clinical trials demonstrate a strong reduction of procollagen type 1 N-terminal propeptide (P1NP) and a moderate reduction of carboxy-terminal collagen crosslinks (CTX), showing that short term effects of intravenous iron-induced hypophosphatemia on bone are primarily driven by FGF23 and consequent hypophoshatemia [9]. These findings suggest that secondary hyperparathyroidism is an unlikely cause of intravenous iron-induced osteomalacia unless associated with severe vitamin D deficiency. However, secondary hyperparathyroidism prior to intravenous iron therapy might predispose to the development of hypophosphatemia and bone disease.

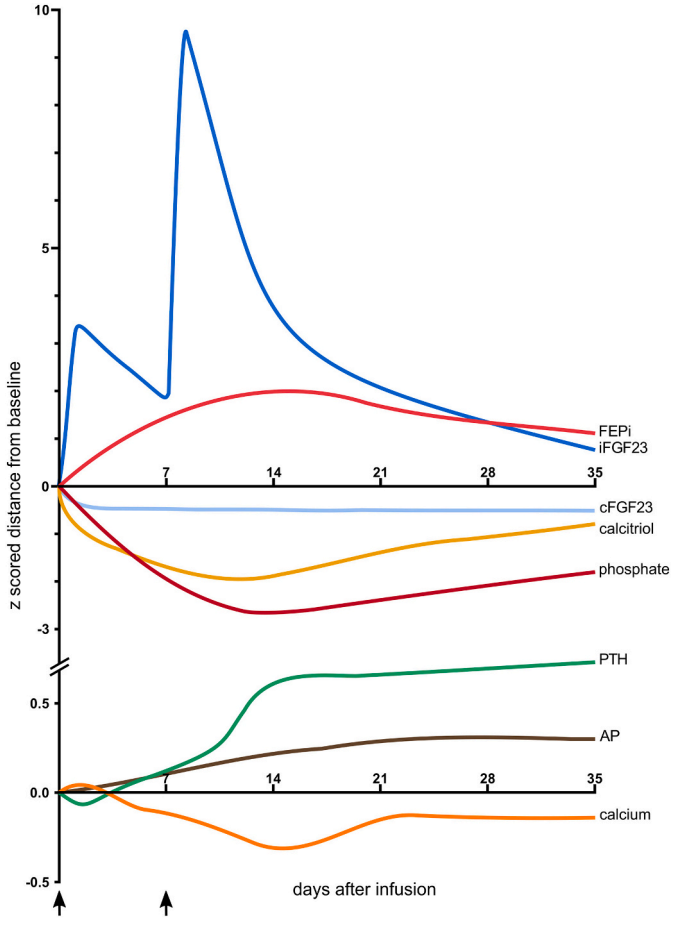

Fig. 2. Schematics of biochemical changes in parameters of bone and mineral metabolism after two doses of 750 mg FCM each on day 0 and day 7 (arrows) over time. Data were extracted from the Phosphare-IDA trial, where parameters were analyzed on day 0, 1, 7, 8, 14, 21, 21, 28 and 35 after the first FCM dose [9]. Data were Z-transformed using the baseline mean concentration and standard deviation of the study cohort and resultant curves were smoothed to illustrate the dynamics over time.

3. Clinical manifestations of intravenous iron-induced hypophosphatemia

The clinical manifestation of high FGF23 with consequent hypophosphatemia is diverse and best known from studies in patients with defects in genes regulating phosphate homeostasis and patients with tumor-induced osteomalacia [28]. Weakness of proximal muscles, bone pain and osteomalacia are typical manifestations of these diseases [29]. Treatment with certain intravenous iron preparations is a novel cause of inappropriate FGF23 elevation and has been associated with similar symptoms especially after repeated administration of FCM [21,30].

In patients with intravenous iron-induced hypophosphatemia, severe and irreversible complications have been reported, reminiscent of tumor-induced osteomalacia. Despite the high rate of hypophosphatemia after FCM, symptoms attributed to hypophosphatemia were rarely reported as adverse drug reaction in studies, which suggests that hypophosphatemia is asymptomatic and self-limited in the majority of patients [31]. Nevertheless, complications of intravenous iron-induced hypophosphatemia, which are often recognized with considerable delay, have been documented in case reports and case series.

To describe the symptoms and complications of intravenous iron-induced hypophosphatemia we performed a structured literature search to identify relevant publications with case reports of hypophosphatemia after FCM or FDI. We identified 77 patients (46 females) who developed hypophosphatemia following FCM treatment (Supplemental Table S1). The mean age of the 77 patients (46 females) identified from the systematic literature search was 48.9 years. Mean hemoglobin was 9.6 (±2.3) g/dL (reference range females 12–16 g/dL, males 13–18 g/dL) and mean ferritin was 11.8 (±9.5) μg/L (reference range females 30–200 μg/L; males 30–300 μg/L) before FCM treatment, indicating severe iron deficiency. Most patients received more than one infusion (58%) with a mean cumulative iron dose of 7 g per patient. Mean lowest phosphate was 0.36 ± 0.14 mmol/L (1.05 ± 0.43 mg/dL) (reference range 0.8–1.5 mmol/L) and hypophosphatemia persisted for a mean of 31.2 weeks. When patients were grouped by their underlying disease-causing iron deficiency, patients with gastrointestinal or gynecological blood loss were more often reported with symptomatic hypophosphatemia than patients with underlying kidney diseases (Fig. 3). A possible explanation for this observation is that patients with gastrointestinal or gynecological diseases typically present with severe iron deficiency which has been identified as a risk factor for hypophosphatemia after intravenous iron [15]. Additional risk factors could be concomitant calcium malabsorption or vitamin D deficiency with secondary hyperparathyroidism in high-risk populations.

Specific symptoms were reported in 44 individual cases and are summarized in Fig. 4/Table S2. As shown, general weakness, fatigue, bone, and muscle pain as well as osteomalacia with fractures were the most common manifestations. These are also typical symptoms in patients with hypophosphatemia of other causes.

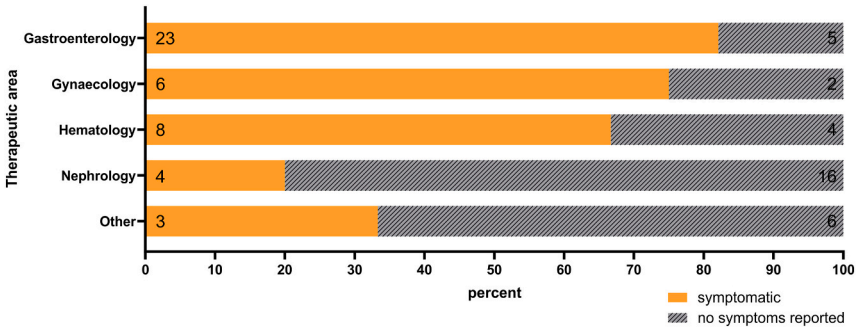

Fig. 3. Symptomatic vs asymptomatic FCM induced hypophosphatemia according to the therapeutic area of 77 case reports. Patients with gynecological or gastrointestinal diseases appeared to have the highest risk for symptomatic hypophosphatemia. Specifically, patients with gastrointestinal blood loss, Osler-Weber-Rendu disease (hematology) or heavy uterine bleeding were commonly reported with symptomatic hypophosphatemia. In contrast, symptoms were rarely reported in patients with underlying kidney disease.

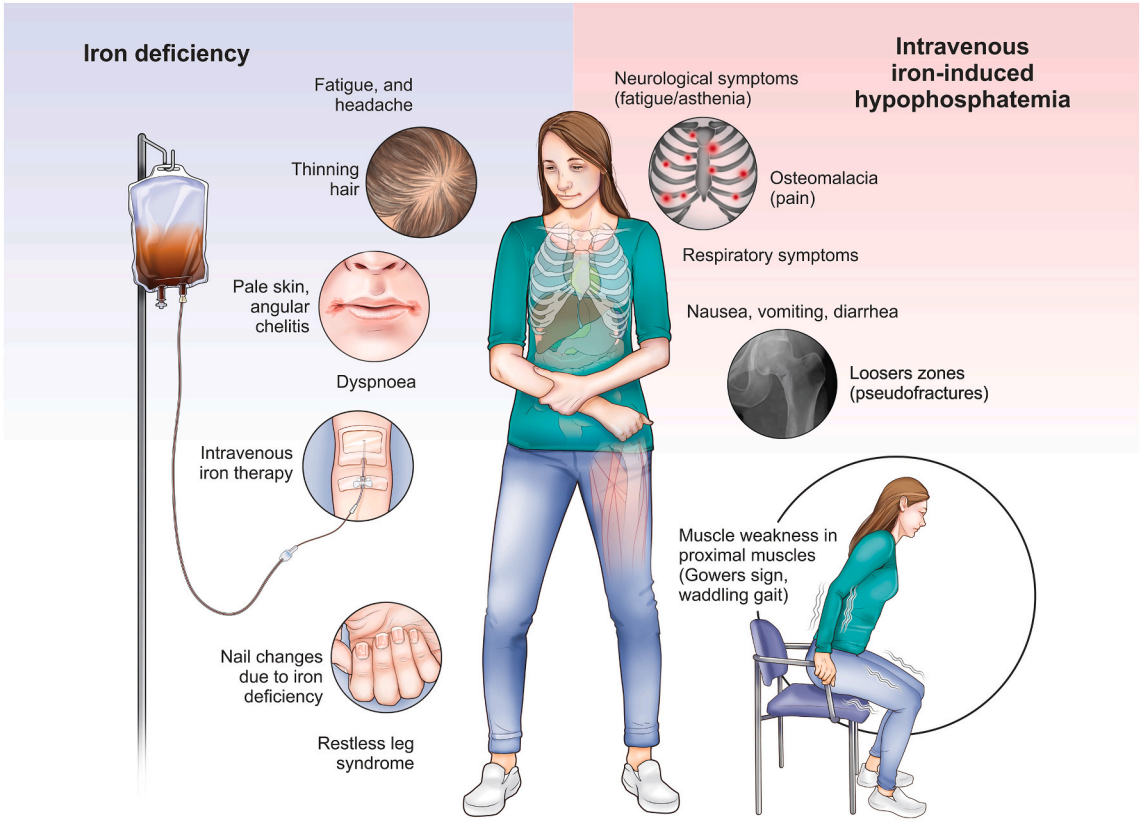

Fig. 4. Manifestations of iron deficiency and intravenous iron-induced hypophosphatemia.

4. Biochemical presentation of patients with intravenous iron induced hypophosphatemia

Prospective studies have shown that FCM-induced hypophosphatemia is triggered by an increase in intact FGF23 that also causes inhibition of vitamin D activation, hypocalcemia and secondary hyperparathyroidism. To determine laboratory changes in markers for bone and mineral metabolism in reported patients with FCM-induced hypophosphatemia, a pooled analysis of laboratory parameters was carried out. To account for differences in reference ranges and explore the magnitude of change each parameter was Z-transformed. As shown in Fig. 5, hypophosphatemia was associated with increased urinary excretion of phosphate in most patients. Mean intact FGF23 was increased, and a majority of cases presented with mild hypocalcemia and hyperparathyroidism. The finding that alkaline phosphatase was increased in most affected patients suggests that high FGF23 is also associated with bone disease [32,33].

5. Recommendations for diagnosis

Treatment and prevention of hypophosphatemia-associated complications require clinical alertness. Considering that mild to moderate hypophosphatemia is asymptomatic and self-limited over the course of several weeks in the majority of patients treated with FCM, we do not recommend universal screening, because this would result in identification of a high number of patients with limited need for specific interventions. Instead of universal screening, we recommend measuring serum phosphate in patients presenting with ongoing or worsening

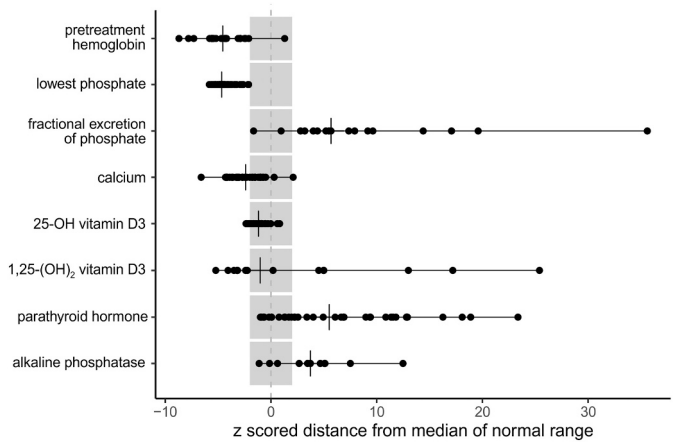

Fig. 5. Summary of biochemical manifestation of hypophosphatemia after FCM in a pooled analysis of cases (n = 68). Pooled results are presented as medians of Z-scores with 95% confidence intervals (see methods section in the supplementary material). Two of five patients with elevated 1,25 $(OH)_2$ vitamin D received treatment with activated vitamin D.

fatigue, bone pain or muscular weakness. Also, in patients requiring repeated infusions of FCM, phosphate should be measured before additional doses are administered. If hypophosphatemia is present, we suggest following the patient until resolution and delaying further doses and switch to iron formulations with lower hypophosphatemia risk [9]. In patients with low phosphate, the fractional excretion of phosphate or TmP/GFR can be assessed to confirm intravenous iron-induced renal phosphate wasting [34]. Outside research settings, FGF23 will be rarely required to confirm the diagnosis of intravenous iron-induced hypophosphatemia. Other changes in mineral metabolism can persist beyond the resolution of hypophosphatemia and gradual return of intact FGF23 to pre-treatment levels. In symptomatic patients a test panel including ionized calcium, total and bone-specific alkaline phosphatase, PTH, 25 (OH) vitamin D and 1,25 $(OH)_2$ vitamin D is recommended. Typical findings in patients with intravenous iron-induced hypophosphatemia include mild hypocalcemia, normal or mildly reduced 25 (OH) vitamin D and markedly reduced 1,25 $(OH)_2$ vitamin D with hyperparathyroidism and elevated total and bone-specific alkaline phosphatase. These changes can persist beyond the resolution of hypophosphatemia [27].

Patients with bone pain should also undergo imaging studies. Conventional x-rays can show a coarse trabecular structure and a loss of secondary trabeculae; another finding suggestive of osteomalacia are Looser zones (Fig. 6). The most sensitive imaging modality is whole body bone scintigraphy, with ^{99m}Technetium labelled diphosphonates which typically shows focal lesions with increased diphosphonate uptake in ribs, lumbar spine, pelvis, femur, tibia or metatarsal bone. Looser zones can be diagnosed by magnetic resonance imaging of the bone, but require specific sequences [35,36]. Bone biopsy is not required to confirm osteomalacia, if the biochemical and imaging findings are consistent with the diagnosis [30,35].

5.1. Summary on recommendations for diagnosis

- Measure serum phosphate in patients receiving multiple intravenous iron infusions, ongoing or worsening fatigue, bone pain or muscular weakness.
- Delay further intravenous iron doses and switch to iron formulations with lower hypophosphatemia risk in patients with hypophosphatemia.
- Assess fractional excretion of phosphate (FEPi) or TmP/GFR.
- If FEPi is high or TmP/GFR is low measure ionized calcium, total and bone-specific alkaline phosphatase, PTH, 25 (OH) vitamin D and 1,25 $(OH)_2$ vitamin D.
- Patients with bone pain should undergo imaging studies.

6. Prevention and management of intravenous iron-induced hypophosphatemia

The clinical suspicion for complications of intravenous iron-induced hypophosphatemic osteomalacia should be high in patients with ongoing blood loss in whom iron deficiency cannot be sustainably corrected (e.g. Osler-Weber-Rendu disease, occult gastrointestinal blood loss). These patients have a high risk for complications. In such patients, ongoing iron deficiency possibly drives FGF23 expression [19]. Treatment of the underlying condition causing ongoing blood loss is therefore of paramount importance to prevent complications from intravenous iron-induced hypophosphatemia.

According to recent recommendations from EMA's pharmacovigilance risk assessment committee and the FDA, the risks of FCM therapy should be carefully considered in patients with known bone disease or high fracture risk [37,38]. It is unknown if vitamin D supplementation before FCM administration reduces hypophosphatemia and fracture risk.

No association between concomitant medication and symptomatic hypophosphatemia after FCM was found in our pooled analysis of cases. Relevant pre-medication reported for two or more patients were vitamin D (n = 10), steroid (n = 4) other immunosuppressants (n = 9) calcium (n = 4) and bisphosphonates (n = 4). After diagnosis, treatment was started in the majority of patients including oral (n = 36) or intravenous (n = 20) phosphate, activated vitamin D (n = 21),vitamin D (n = 9) or calcium (n = 10). Treatment outcome was highly variable and inconsistently reported. Considering the underlying pathogenesis driven by elevated intact FGF23, phosphate supplementation would not sustainably correct hypophosphatemia, but increase urinary phosphate excretion [39–41]. As clinical and biochemical changes apparently persist up to several months after the last FCM infusion, rational treatment approaches would include mitigation of secondary hyperparathyroidism with activated vitamin D, which was successfully used in some patients [40,42,43]. In addition, high FGF23 could be directly inhibited with the therapeutic anti-FGF23 antibody burosumab which is not licensed for this indication. This treatment approach has been successfully used in one patient, and can be considered a contingency strategy in severe cases [44]. A calcimimetic, such as cinacalcet, is effective in treating tumor-induced osteomalacia but it is not approved for this use nor has it been used for cases of intravenous iron-induced osteomalacia [45].

7. Conclusion & perspective

In conclusion, hypophosphatemia is a common medical problem after administration of FCM. The summary of symptoms and biochemical findings reported here represents a structured description of the potential clinical presentation of intravenous iron-induced hypophosphatemia and as such guides clinicians to recognize the complications and react accordingly.

Disclosures

Dr. Schaefer reported receiving personal fees from Pharmacosmos A/S, and Vifor Pharma, and grants and personal fees from AbbVie, and Gilead outside the submitted work.

Dr. Zoller reported receiving grants, personal fees, and nonfinancial support from AbbVie, Gilead, Pharmacosmos A/S, and Vifor Pharma; personal fees from Merck; personal fees and nonfinancial support from Bayer; grants from Merck Sharp & Dohme; and honoraria for lecturing from Bristol-Myers Squibb, Medice, Merz, and Novartis outside the submitted work.

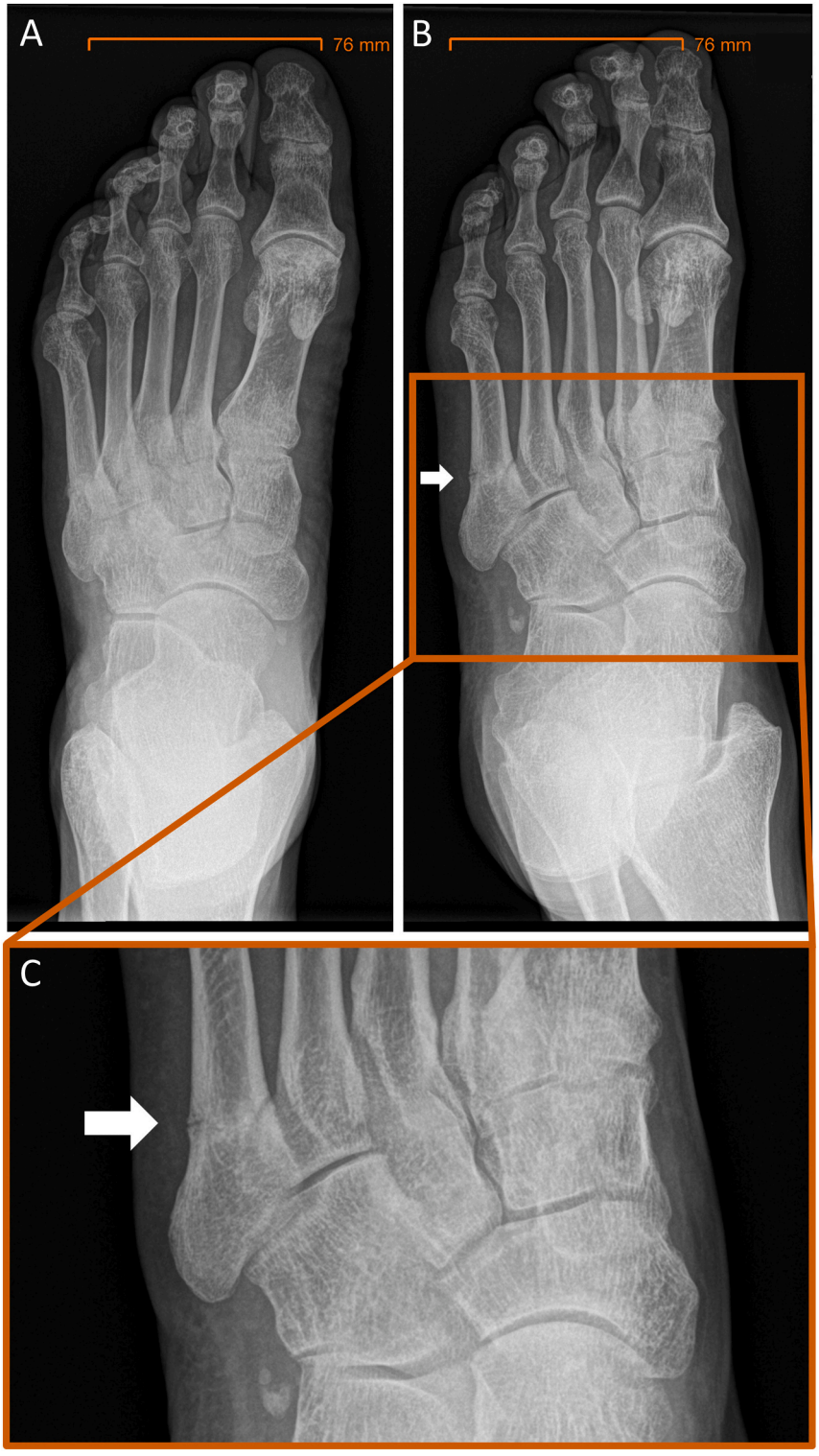

Fig. 6. Atypical proximal fracture of the left fifth metatarsal bone (Looser zone indicated by the white arrow) which becomes clearly visible only after rotation of the foot. The patient presented with pain and was unable to walk after repeated infusions of ferric carboxymaltose. At the time of presentation the patient was hypophosphatemic and presented with osteomalacia as shown by conventional x-ray of the foot. (A) Dorsoplantar x-ray. (B) Oblique x-.ray axis. (C) Enlargement of (B).

Dr. Wolf reported receiving personal fees from Akebia, Ardelyx, AstraZeneca, Bayer, Jnana, Pharmacosmos A/S, Unicycive, and Walden Biosciences outside the submitted work.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2021.116202.

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