

FGF23 Elevation and Hypophosphatemia after Intravenous Iron Polymaltose: A Prospective Study

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Context: Parenteral iron administration has been associated with hypophosphatemia. Fibroblast growth factor 23 (FGF23) has a physiological role in phosphate homeostasis via suppression of 25-hydroxyvitamin D [25(OH)D] activation and promotion of phosphaturia. We recently reported a case of iron-induced hypophosphatemic osteomalacia associated with marked FGF23 elevation.

Objective: Our objective was to prospectively investigate the effect of parenteral iron polymaltose on phosphate homeostasis and to determine whether any observed change was related to alterations in circulating FGF23.

Design, Setting, and Participants: Eight medical outpatients prescribed iv iron polymaltose were recruited. Plasma phosphate, 25(OH)D, 1,25-dihydroxyvitamin D [1,25(OH)₂D], PTH, FGF23, and urinary tubular reabsorption of phosphate were measured prior to iron administration and then weekly for a minimum of 3 wk.

Results: Plasma phosphate fell from 3.4 ± 0.6 mg/dl at baseline to 1.8 ± 0.6 mg/dl at wk 1 ($P < 0.0001$) associated with a fall in percentage tubular reabsorption of phosphate (90 ± 4.8 to 68 ± 13 ; $P < 0.001$) and 1,25(OH)₂D (54 ± 25 to 9 ± 8 pg/ml; $P < 0.001$). These indices remained significantly suppressed at wk 2 and 3. 25(OH)D levels were unchanged. FGF23 increased significantly from 43.5 pg/ml at baseline to 177 pg/ml at wk 1 ($P < 0.001$) with levels correlating with both serum phosphate ($R = -0.74$; $P < 0.05$) and 1,25(OH)₂D ($R = -0.71$; $P < 0.05$).

Conclusion: Parenteral iron suppresses renal tubular phosphate reabsorption and 1 α -hydroxylation of vitamin D resulting in hypophosphatemia. Our data suggest that this is mediated by an increase in FGF23. (*J Clin Endocrinol Metab* 94: 2332–2337, 2009)

Inorganic phosphate is the major driving force for mineralization of newly formed osteoid with chronic hypophosphatemia causing osteomalacia in adults and rickets in children. It is also an essential component of cell membrane phospholipids, nucleic acids, and phosphorylated enzymes and it serves as a buffer for body pH. Systemic effects of prolonged phosphate deficiency result from reduced AMP and 2,3 diphosphoglycerate levels and include muscle weakness, myocardial dysfunction, respiratory failure, and abnormal erythrocyte, leukocyte, and platelet function (1, 2).

Plasma phosphate concentration is determined by dietary intake, intestinal absorption, renal tubular reabsorption, and shifts

between the intracellular and extracellular space. The kidney is the most important regulator of phosphate homeostasis with rapid adjustments in renal excretion under altered physiological conditions. At steady state, 80–90% of filtered phosphate is reabsorbed, principally via type IIa sodium phosphate cotransporters in the proximal tubule, with this approaching 100% within hours of hypophosphatemia due to an increase in cotransporter protein expression (3).

Over the past decade, our understanding of phosphate homeostasis has increased through the identification of phosphatonins, circulating factors that both reduce sodium phosphate cotransporter numbers and suppress expression of renal 25-hy-

droxyvitamin D [25(OH)D] 1 α -hydroxylase (4, 5). The phosphatonin fibroblast growth factor 23 (FGF23) is secreted from osteocytes and osteoblasts (6, 7) and is detectable in the circulation of healthy individuals, where it is positively correlated with changes in serum phosphate (8, 9). Increased concentrations of this peptide hormone are responsible for the altered phosphate regulation seen in autosomal dominant hypophosphatemic rickets, X-linked hypophosphatemic rickets (XLH), autosomal recessive hypophosphatemic rickets, tumor-induced osteomalacia (TIO), and selected cases of McCune-Albright syndrome (7, 10, 11).

Parenteral iron administration has been associated with hypophosphatemia and osteomalacia (12–16). This complication is neither widely appreciated nor acknowledged in reviews on iron therapy or in product information sheets. The condition is characterized by reduced renal phosphate reabsorption and inhibition of 1 α -hydroxylation of vitamin D (12, 13), which suggests that phosphatonins may play an etiological role. In support of this possibility, we have recently reported the first case of iron-induced hypophosphatemic osteomalacia associated with significant FGF23 elevation (14).

This study was a hypothesis-driven examination of the mechanism of iron-induced hypophosphatemia with the aim of prospectively assessing the effect of a single infusion of iron polymaltose on plasma phosphate and FGF23 levels in ambulatory medical outpatients. Our hypotheses were that: 1) parenteral iron predictably decreases tubular reabsorption of phosphate (TRP) and serum phosphate; and 2) the changes in phosphate homeostasis are directly related to alterations in circulating FGF23.

Patients and Methods

Participants

Patients prescribed an outpatient infusion of iron polymaltose as part of routine medical care were recruited from the day unit at Christchurch Public Hospital (Christchurch, New Zealand). Exclusion criteria were: 1) glomerular filtration rate less than 60 ml/min/1.73 m²; 2) history of hypophosphatemia, hypo- or hyperparathyroidism; 3) high-dose steroid use; and 4) use of medications potentially altering phosphate homeostasis. The study was approved by the New Zealand Upper South B Regional Ethics Committee, and informed written consent was obtained from all patients.

Eight iron-deficient female patients, aged 21 to 84 yr (mean, 45 yr), were followed prospectively. Five patients had previously experienced significant gastrointestinal side effects, and three had an inadequate hemoglobin response to oral iron. Three patients had Crohn's disease, two had celiac disease, and in three, extensive investigations had failed to determine a cause for their iron deficiency. Two patients had previously received parenteral iron, their last infusion occurring more than 3 months before study inclusion. Iron polymaltose (Ferrosig; Sigma Pharmaceuticals, Victoria, Australia) containing 500–1600 mg (mean, 918 mg) of elemental iron was administered as a single infusion in normal saline over 4–5 h. This preparation contains 218 mg polymaltose for every 100 mg elemental iron. Patients' medications were unchanged for the duration of the study, and no individual received phosphate or calcitriol therapy. Dietary phosphate intake was not assessed.

Biochemical measurements

Blood and urine samples were obtained in the morning after an overnight fast at baseline, immediately before an infusion of iron polymaltose, and weekly for a minimum of 3 wk after infusion. Plasma phosphate, calcium, albumin, and creatinine and urinary phosphate and creatinine were determined by standard clinical methods. Percentage TRP was calculated from the phosphate/creatinine clearance ratio. Blood collected in EDTA tubes was immediately centrifuged, separated, and frozen at –25 C and was later assayed for FGF23, PTH, 25(OH)D, and 1,25-dihydroxyvitamin D [1,25(OH)₂D]. FGF23 concentrations were measured in duplicate using a two-site intact ELISA assay (Kainos Laboratories, Tokyo, Japan) according to manufacturer's specifications. The intraassay coefficient of variation (CV) was 7.3%, interassay CV was less than 5%, lower limit of detection was 3 pg/ml, and upper maximal detectable concentration was 800 pg/ml. A two-site automated ELISA assay (Roche Elecsys 2010; Roche, Basel, Switzerland) was used to measure plasma PTH with inter- and intraassay CVs of 3.4 and 1.9%, respectively, at 7 pmol/liter. 25(OH)D was analyzed after hexane extraction and reconstitution in 70% aqueous methanol by HPLC-tandem mass spectrometry using a Shimadzu 20 series HPLC system with a C8 reverse phase column coupled to a API 3200 Q-trap tandem mass spectrometer (Applied Biosystems, Foster City, CA). The intraassay CV was 10.2%. 1,25(OH)₂D was determined by RIA (Immunodiagnosics Systems Limited) with low and high quality control values (and interassay CV) of 40.7 (10.1%) and 131.4 (12.4%) pmol/liter and intraassay CV below 12%. Automated two-site electrochemiluminescence immunoassays (Roche Diagnostics, Mannheim, Germany) were used to measure C-telopeptide, osteocalcin, and amino-terminal propeptide of type 1 procollagen (P1NP). The lower limits of assay detection were 0.01, 0.5, and 5 ng/ml, respectively. Interassay CVs were 6.1% at 7 ng/ml for C-telopeptide, 6.5% at 16 ng/ml for osteocalcin, and 2.9% at 60 ng/ml for P1NP. Intraassay CVs were 1.8% at 0.39 ng/ml for C-telopeptide, 4% at 16 ng/ml for osteocalcin, and 2.3% at 60 ng/ml for P1NP.

Urinary amino acids (alanine, arginine, citrulline, cystine, glutamic acid, glutamine, glycine, isoleucine, leucine, methionine, ornithine, phenylalanine, serine, threonine, tyrosine, and valine) were quantified as a marker of proximal tubular damage. Urine samples were prepared in Uriprep (Pickering Laboratories, Mountain View, CA), and amino acids were quantified using ion-exchange liquid chromatography (Dionex, Sunnyvale, CA) followed by post column ninhydrin derivatization (Pickering Laboratories).

Statistical analysis

Results are expressed as mean \pm SD or as median (interquartile range), as appropriate. Logarithmic transformation was performed on skewed variables to obtain a normal distribution before statistical computations. Mean levels were compared between time points using repeated measures ANOVA. When this indicated a significant effect of time, this was further explored by comparing biochemical measurements at baseline with levels at wk 1–3 using Fisher's protected least significant difference test. Mean values after wk 3 were not calculated because only those patients with persisting hypophosphatemia were being assessed. A *P* value < 0.05 was considered statistically significant. No adjustment was made for multiple testing of 11 different measures. Pearson correlation coefficient was used to examine the relationship between continuous variables.

Results

Biochemical indices of mineral metabolism at baseline and at weekly intervals after an iron polymaltose infusion are shown in Table 1. Phosphate and percentage TRP values were within the reference range at baseline in all individuals, with mean levels of 3.4 \pm 0.6 mg/dl and 90 \pm 4.8%, respectively. As shown in Fig. 1,

TABLE 1. Biochemical indices at baseline and after a single infusion of iron polymaltose

	Baseline	Wk 1	Wk 2	Wk 3	P value* (ANOVA)	Reference range
Phosphate (mg/dl)	3.4 ± 0.6	1.8 ^a ± 0.6	1.8 ^a ± 0.6	1.9 ^a ± 0.6	<0.001	2.5–4.3
Calcium (mg/dl)	9.2 ± 0.2	9.1 ± 0.4	9.0 ± 0.3	9.0 ± 0.5	0.16	8.8–10.4
Creatinine (mg/dl)	0.87 ± 0.11	0.86 ± 0.10	0.89 ± 0.14	0.84 ± 0.11	0.14	0.57–1.24
% TRP	90 ± 4.8	68 ^b ± 13	68 ^c ± 15	69 ^c ± 18	<0.001	
25(OH)D (ng/ml)	27 ± 5	23 ± 6	26 ± 8	28 ± 8	0.24	20–60
1,25(OH) ₂ D (pg/ml)	54 ± 25	9 ^b ± 8	18 ^c ± 17	29 ^d ± 21	<0.001	27–73
PTH (pg/ml)	28 (23–44)	27 (20–40)	34 (26–49)	54 (34–64)	0.001	14.5–63.6
C-telopeptide (ng/ml)	0.32 ± 0.26	0.26 ± 0.17	0.26 ± 0.18	0.33 ± 0.22	0.037	<0.75
P1NP (ng/ml)	52.4 ± 31.1	38.9 ^d ± 22.9	35.6 ^c ± 21.5	38.1 ^d ± 21.7	0.001	15–76
Osteocalcin (ng/ml)	24.5 ± 12.2	18.3 ^c ± 9.0	17.5 ^c ± 9.8	17.2 ^c ± 9.2	<0.001	11–70
FGF23 (pg/ml)	43.5 (38.8–49.9)	177 ^b (119–260)	93.4 ^c (68.2–154)	68.8 (45.5–114)	<0.001	<71

Results are expressed as mean ± SD or median (interquartile range) for skewed variables. Multiplication factors to convert to SI units are as follows: phosphate, × 0.3229; calcium, × 0.25; creatinine, × 88.4; 25(OH)D, × 2.496; 1,25(OH)₂D, × 2.4; and PTH, × 0.11.

* P values from repeated-measures ANOVA "time" effect are listed.

^a P < 0.0001; ^b P < 0.001; ^c P < 0.01; and ^d P < 0.05 for comparisons to baseline by *post hoc* Fisher's protected least significant difference test.

there was a fall in plasma phosphate at wk 1, with seven of eight patients becoming hypophosphatemic. Mean phosphate levels were significantly lower than baseline at wk 1–3, with persisting hypophosphatemia at wk 6 in two patients. Normalization of phosphate over time was demonstrated in all but one patient who was unavailable for blood tests after wk 6. All patients demonstrated suppression of percentage TRP (Fig. 2A) with trough values of 32–75%. Similar to plasma phosphate, mean percentage TRP remained significantly suppressed at wk 1–3. There was no significant change in serum creatinine during the study, and quantitative analysis of urinary amino acids when patients were hypophosphatemic was normal.

25(OH)D levels did not change significantly during the study; however, 1,25(OH)₂D fell from a mean of 54 pg/ml at baseline to 9 pg/ml at wk 1 (Fig. 2B). One patient showed full suppression of 1,25(OH)₂D production, with an undetectable value at wk 1 (<4.2 pg/ml) compared with 76 pg/ml before their iron infusion. The suppression of 1,25(OH)₂D remained significant compared with baseline at wk 2 and 3. PTH levels rose with values trending above baseline at wk 3, although this did not reach statistical significance (P = 0.08). A fall in the bone formation markers osteocalcin and P1NP was noted at wk 1, with persisting suppression at wk 3 compared with baseline. Although repeated-measures ANOVA suggested a difference in mean C-telopeptide concentration over time, no significant difference was noted between baseline and subsequent weeks when this was further evaluated using Fisher's protected least significant difference test.

Baseline FGF23 levels were all within the previously established assay reference range. Increased levels were seen in all patients at wk 1 after iron polymaltose (Fig. 2C) with a striking mean increase of 455% (range, 74–1189%). Levels remained significantly elevated at wk 2. Four of eight individuals had FGF23 levels persistently above the upper limit of the reference range at wk 3. In one patient, peak FGF23 was dramatically elevated at over 12-fold baseline (640.5 pg/ml). This elevation was prolonged, with FGF23 increased 7-fold baseline at wk 3 (357.2 pg/ml) and still above the reference range at wk 5 (90.2 pg/ml). This correlated with prolonged suppression of renal phosphate reabsorption with persisting hypophosphatemia at wk 6.

There was no correlation between cumulative or current iron dose and peak FGF23 levels. Serum phosphate at wk 1 was negatively correlated with FGF23 at the same time point (R = -0.74; P < 0.05). The decline in 1,25(OH)₂D was correlated with both the change in FGF23 and peak FGF23 (R = -0.80 and R = -0.71, respectively; P < 0.05).

Discussion

This study shows that a single infusion of iron polymaltose predictably causes significant and prolonged FGF23 elevation, accompanied by a decrease in plasma phosphate, renal phosphate wasting, and suppression of 1,25(OH)₂D.

Hypophosphatemia complicating administration of parenteral iron was first reported in 1982 in the Japanese literature (15). In 1983, Okada *et al.* (16) documented a temporary fall in serum phosphate and percentage TRP during treatment with iron sucrose, and two subsequent studies reported a fall in 1,25(OH)₂D levels despite normal 25(OH)D, suggesting an inhibitory effect of parenteral iron on 25(OH)D 1 α -hydroxylase activity (12, 13). Our findings are consistent with these previous reports and in addition describe the novel etiologic role of FGF23 in this condition.

It has been suggested that iron may have a direct toxic effect on renal tubular cells (12, 13). Nephrotoxicity is seen with other heavy metals including cadmium, mercury, and lead with the extent of renal damage dependent on the dose, route of administration, and exposure duration. Although the pattern of acute toxicity differs between metals, chronic intoxication typically induces a generalized proximal tubular disorder (Fanconi syndrome) (17). Our study does not, however, support nephrotoxicity as the cause for renal phosphate wasting because urinary amino acid excretion was normal at a time when phosphaturia was maximal, suggesting a specific proximal tubular defect related to phosphate homeostasis. Furthermore, if tubular damage was the primary inciting event, then the resulting fall in phosphate would be expected to suppress FGF23 levels, in direct contrast to our findings.

One week after parenteral iron, all patients in our study had FGF23 levels above the previously established assay reference

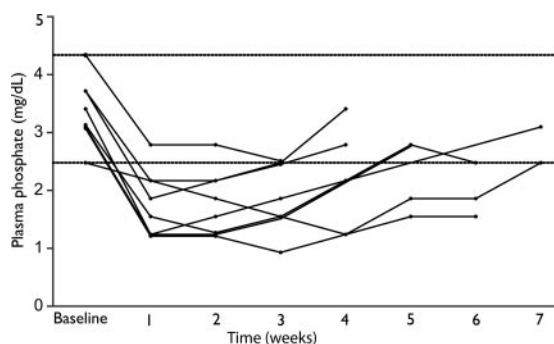


FIG. 1. Plasma phosphate immediately before and at weekly intervals after parenteral iron polymaltose. The normal phosphate range is indicated with horizontal dashed lines.

range (18). The degree of elevation was dramatic, with levels similar to those seen in autosomal dominant hypophosphatemic rickets, XLH, and TIO (19, 20). Due to our study design, with biochemical indices of phosphate metabolism being first assessed

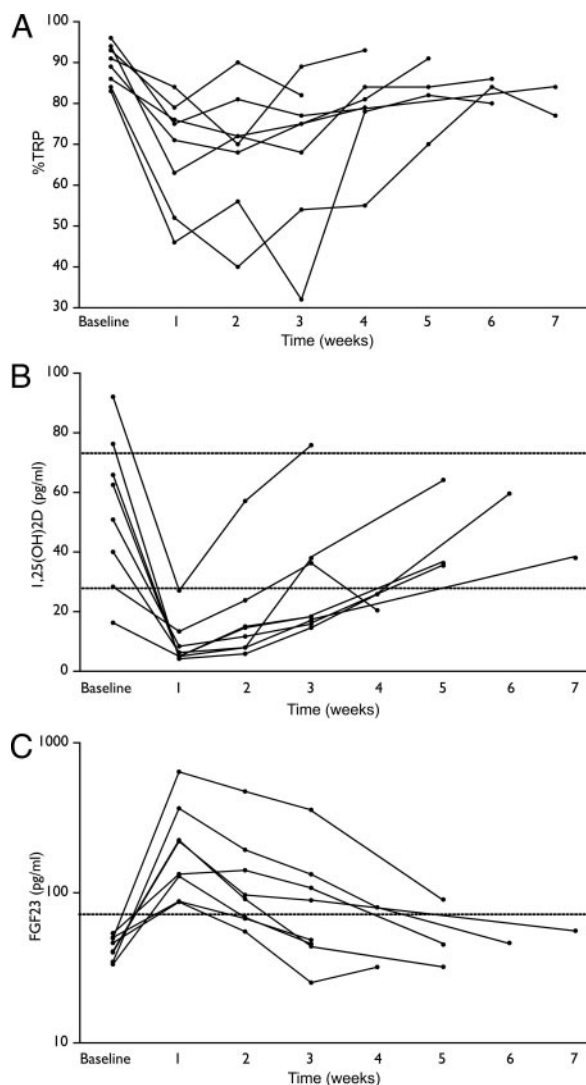


FIG. 2. Percentage TRP (A), 1,25(OH)₂D (B), and FGF23 (C) at baseline and after parenteral iron polymaltose. The FGF23 reference range falls below and 1,25(OH)₂D reference range falls between the dashed lines. %TRP reference range is dependent on serum phosphate and in hypophosphatemia should approach 100%.

1 wk after iron administration, it is likely that peak FGF23 was missed, and further investigations with more frequent plasma measurements are required to determine the rapidity and extent of FGF23 increase. The elimination half-life of intact FGF23, determined in patients undergoing resection of FGF23-producing mesenchymal tumors, has been calculated to be 58 ± 34 min (21). The prolonged elevation of plasma FGF23 seen in our cohort after the iron infusion (mean FGF23 still significantly elevated at wk 2, with one patient having a level 230% baseline at wk 5) is of interest. The mechanism underlying these changes in circulating FGF23 remains speculative but may involve up-regulation of synthesis or secretion, reduction in clearance of the intact molecule, posttranslational modification affecting the cleavage site, or possibly inhibition of proteolytic cleavage. In support of the latter hypothesis, Durham *et al.* (22) recently reported elevated C-terminal FGF23 (Immutopics, San Clemente, CA) in patients with low serum ferritin. This suggests that iron may regulate the rate of enzymatic cleavage of intact FGF23, with increased levels inhibiting and iron deficiency increasing protease activity.

Klotho, a transmembrane protein that acts as a cofactor for and determines the tissue specificity of FGF23, is predominantly present in tissues that regulate calcium homeostasis including the renal tubules, choroid plexus, and parathyroid glands. Animal and *in vitro* studies have shown parathyroid FGF23-klotho receptor activation to suppress PTH gene expression and secretion (23, 24). This effect does not appear to be clinically significant, however, with high PTH in the setting of FGF23 elevation seen in TIO, XLH, and chronic renal failure (25, 26), most probably a compensatory response to maintain eucalcemia in the setting of 1,25(OH)₂D suppression. In our study, PTH increased over the first 3 wk, although not reaching statistical significance.

Recent reports suggest that FGF23 may have a phosphate-independent effect on bone. Wang *et al.* (27) demonstrated suppression of osteoblast differentiation and matrix mineralization in a fetal rat calvaria cell line overexpressing FGF23, and Sitara *et al.* (28) have reported defective bone mineralization in cultured mouse osteoblasts exposed to FGF23-containing medium. A significant drop in the osteoblast protein products osteocalcin and P1NP was demonstrated in our study and is in accordance with this *in vitro* data. Whether these effects are clinically significant in humans is unknown; however, it is important to note that calcitriol, commonly prescribed together with phosphate in hypophosphatemia, increases FGF23 in a dose-dependent fashion (29, 30). Current therapy in FGF23-associated hypophosphatemia may therefore be inadequate to prevent long-term skeletal complications.

Iron is complexed with a carbohydrate ligand (dextran, sucrose, gluconate, or polymaltose) to form a colloidal suspension for iv administration. The amount of polymaltose infused in our study cohort ranged from 1.1 to 3.5 g. Although we hypothesize that the iron fraction is responsible for the elevation of FGF23 and development of hypophosphatemia, we acknowledge that a limitation of our study is the absence of a control group receiving polymaltose only. It is known that insulin-stimulated glycolysis after oral or iv carbohydrate increases intracellular phosphate demand. The increased synthesis of phosphorylated intermediates results in redis-

tribution of phosphate into the intracellular compartment with a fall in plasma phosphate levels (31, 32). This effect has been shown to be short-lived, with normalization of plasma phosphate within 2 h of a meal (32), and is accompanied by a reduction in fractional urinary phosphate excretion (33). Thus, the prolonged hypophosphatemia and development of phosphaturia seen in our study cohort is not consistent with a carbohydrate effect.

An additional limitation of our study is that we assessed the effect of parenteral iron on multiple biochemical indices, thereby increasing the risk of a type 1 statistical error. The measured indices were not all independent however, and importantly, our study was hypothesis driven, based on recent clinical observation (14).

Parenteral iron is being increasingly prescribed with little awareness of the potential for hypophosphatemia. Indications to switch from oral iron include intolerable side effects or an inadequate hemoglobin response due to malabsorption, active gastrointestinal bleeding, or noncompliance. Intravenous iron therapy is now standard of care in patients with chronic renal failure on erythropoietin and improves hemoglobin response when administered with erythropoietin in patients with anemia of cancer and cancer chemotherapy (34, 35). Proponents of this therapy are advocating increased use in anemia of chronic inflammation (36, 37), a condition in which up-regulation of the hepatic hormone hepcidin causes functional iron deficiency by reducing oral iron absorption and blocking iron release from macrophages and hepatocytes (38). While acknowledging the association between high molecular weight iron dextran and anaphylactoid reactions, reviews on parenteral iron have stated that it is underutilized and claim that when high molecular weight dextran iron is excluded, this therapy is not associated with an increased risk of adverse events (39). However, both iron polymaltose and sucrose have been associated with hypophosphatemia with case reports of osteomalacia complicating prolonged use (12–15).

This is the first study to implicate FGF23 in the development of hypophosphatemia after parenteral iron administration. Although the true incidence remains unknown, our results suggest that this is a common phenomenon. We recommend that patients receiving long-term parenteral iron infusions are screened for this complication because timely intervention may minimize the risk of osteomalacia and prevent patient morbidity. Whereas the use of oral 1,25(OH)₂D and phosphate supplements may be beneficial acutely in patients with severe symptomatic hypophosphatemia, avoidance of further parenteral iron is advocated in patients with hypophosphatemic osteomalacia given the potential negative direct effect of FGF23 on the skeleton. The exact mechanism by which iron therapy disrupts FGF23 metabolism requires further study.

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