Hypophosphataemia after ferric carboxymaltose is unrelated to symptoms, intestinal inflammation or vitamin D status

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Abstract

Background and aims

Intravenous iron replacement is recommended for iron-deficient patients with inflammatory bowel disease (IBD), but may be associated with hypophosphataemia, predisposing to osteomalacia and fractures. This study aimed to evaluate the incidence and risk factors for hypophosphataemia following intravenous ferric carboxymaltose (FCM) in patients with IBD.

Methods

This prospective observational study of patients with and without IBD evaluated serum phosphate for 28 days following intravenous FCM, and assessed associations with symptoms, markers of inflammation and vitamin D status.

Results

24 patients with IBD (11 with Crohn's disease [CD], 13 with ulcerative colitis [UC], mean age 45 years [range 19-90], 7 female), and 20 patients without IBD (mean age 56 [22-88]y, 11 female), were included. Overall, serum phosphate declined by a mean of 36% at Day 7, with a mean fall of 42% (SD 19%) at some time point over 28 days ($p < 0.001$). Twenty-four of 44 (55%) patients developed moderate to severe hypophosphataemia (serum phosphate < 0.6 mmol/L). No differences between patients with and without IBD were seen, but patients with CD had greater decline in phosphate than those with UC. There was no association between hypophosphataemia and symptomatic adverse events, faecal calprotectin, C-reactive protein, albumin, platelet count, 25(OH) vitamin D, or 1,25(di-OH) vitamin D. Intact fibroblast growth factor levels increased by mean 84% ($p = 0.004$), within 2 days of infusion. Serum phosphate < 1.05 mmol/L on Day 2 predicted susceptibility to moderate-severe hypophosphataemia (OR 7.0).

Conclusions

Hypophosphataemia following FCM is common, unrelated to symptomatic adverse events, baseline intestinal or systemic inflammation, or vitamin D status.

Introduction

Iron deficiency, with or without anaemia, is one of the commonest systemic complications in patients with inflammatory bowel disease (IBD), affecting between 13 and 90% of patients.[1–4] Iron deficiency anaemia in patients with IBD is considered a marker of disease activity, and is associated with a reduced quality of life, impaired cognition and social functioning, and an increased risk of hospitalisation.[5–7] Recognition and correction of iron deficiency independent of IBD activity is associated with an improvement in these parameters,[7, 8] and intravenous iron is recommended for patients with moderate to severe anaemia or intolerance to oral iron formulations.[2, 4, 5, 9]

Modern intravenous iron formulations are considered safe in patients with IBD, with treatment-related adverse events described in 10–30% of patients, including nasopharyngitis, headaches, back pain, nausea or flu-like symptoms.[10–14]

Hypophosphataemia following intravenous iron, especially following ferric carboxymaltose (FCM), is increasingly recognised, likely mediated by a transient increase in intact fibroblast growth factor-23 (iFGF-23) due to inhibition of its cleavage, which results in phosphaturia.[15–17] When recurrent or persistent, this may result in osteomalacia and fractures.[16, 18]

Of particular relevance to patients with IBD, repeated iron infusions, malnutrition and vitamin D deficiency may aggravate risk of hypophosphataemia.[19] Furthermore, iFGF-23 is upregulated by systemic inflammation, which may, theoretically, be a further risk factor for hypophosphataemia in patients with IBD.[20] This study aimed to prospectively evaluate the incidence and severity of intravenous FCM-associated hypophosphataemia in patients with and without IBD, its association with symptoms, and ascertain associated risk factors including systemic and intestinal inflammation, and vitamin D status, to enable potential preventative strategies.

Materials And Methods

Subjects

Consecutive non-pregnant iron-deficient patients with and without IBD attending a tertiary gastroenterology unit, who were deemed to require intravenous FCM, were invited to participate.

Protocol and analytical assays

One gram FCM was administered to all patients. Baseline demographics and disease characteristics, haematological and biochemical indices, 25(OH) vitamin D and serum for analysis of iFGF-23, c-terminal FGF-23 (cFGF-23, the cleaved fragment of iFGF-23) and vitamin D binding protein (DBP), were collected. Faecal samples were analysed for calprotectin by fluorescence enzyme immunoassay (Phadia 100 EliA™ Calprotectin, Thermo Scientific, Scoresby, Australia). Clinical and biochemical assessment was repeated 2, 4, 7, 14 and 28 days after infusion, including direct questioning of gastrointestinal symptoms and adverse events, and serum stored for analysis of iFGF-23 and cFGF-23 at Days 2, 7 and 28.

Serum iFGF-23 was analysed in duplicate by enzyme-linked immunosorbent assay (ELISA, Kainos, Shizuoka, Japan), as previously described.[21] Serum cFGF-23 was analysed in duplicate by ELISA (Immunotopics, San Clemente, CA, USA), as described previously.[21]

Endpoints

The endpoints for this study included mean reduction in serum phosphate levels from Day 0 to Day 7, the proportion of patients experiencing a moderate (Grade 3, serum phosphate < 0.6 mmol/L) to severe (Grade 4 toxicity, < 0.3 mol/L) hypophosphataemia[22] at any stage during the follow-up period,

difference in rate of hypophosphataemia between patients with and without IBD, and association of hypophosphataemia with degree of systemic (CRP) or intestinal (faecal calprotectin) inflammation, and serum vitamin D status. Additionally, the correlation between hypophosphataemia and symptomatic adverse events was evaluated.

Statistical analyses

Results were analysed by SPSS v23 (IBM Corp) and Graphpad Prism v6 (GraphPad Software, Inc, California, USA) using paired and unpaired t-tests, Fisher's exact test, and multiple regression analyses as appropriate. A two-tailed p-value of < 0.05 was considered statistically significant for all associations.

Ethical considerations

The protocol for this study was approved by the Office of Research and Ethics at Eastern Health (LR 17-2017, approved 17 March 2017), and was performed in accordance with Australian regulations and the principles of the Declaration of Helsinki 1954 and its later amendments. Written, informed consent was obtained from all participants included in this study.

Results

Twenty-three non-IBD controls and 27 patients with IBD were recruited. Three patients from each group were excluded due to loss of follow-up within one week following infusion, leaving 24 patients with IBD (11 with Crohn's disease [CD] and 13 with ulcerative colitis [UC]) and 20 non-IBD controls for analysis (Table 1). Characteristics of disease in patients with IBD are shown in Table 2.

Table 1
Baseline participant characteristics.

	IBD (n = 24)	Non-IBD Controls (n = 20)	P value [†]
Age (mean +/- range)	45 (19–90)	56 (22–88)	0.045
Female:Male	7:17	11:9	0.153 [‡]
Co-morbid illnesses, n (%)			
Type 2 diabetes mellitus	2	3	
Chronic kidney disease	1	0	
Atrial fibrillation	1	0	
Ischaemic heart disease	1	2	
Colorectal adenocarcinoma	0	1	
Other cancer	1	3	
Body mass index (mean +/- range)	26.9 (17.6–51.3)	26.5 (5.43)	0.866
Haemoglobin (g/L, mean, range)	121 (62–153)	124 (86–162)	0.597
MCV (10 ⁻¹⁵ L, mean, range)	82 (55–96)	81 (68–88)	0.601
Serum ferritin (ng/mL, mean, range)	30 (3–93)	25 (7–62)	0.395
White cell count (X 10 ⁹ /L, mean, range)	7.6 (4.0-10.9)	6.8 (3.7–21.4)	0.416
Platelet count (x 10 ⁹ /L, mean, range)	318 (150–680)	237 (143–366)	0.009
eGFR (mL/min/1.73 m ² , mean, range)	85 (38 - >90)	80 (45->90)	0.273
Serum albumin (g/L, mean, range)	35 (25–48)	38 (30–50)	0.064
Serum C-reactive protein (mg/L, median, range)	16 (2–43)	19 (5–48)	0.417
Faecal calprotectin (µg/g, median, range)	573 (< 15- >3000)	47 (< 15–300)	0.023
25(OH) vitamin D (nmol/L, mean, range)	51 (8-104)	49 (20–96)	0.822
1,25(di-OH) vitamin D (pmol/L, mean, range)	112 (50–202)	136 (62–263)	0.109

[†]Unpaired t-test unless otherwise specified.

[‡]Chi-square

	IBD (n = 24)	Non-IBD Controls (n = 20)	P value [†]
Serum calcium (corrected, mmol/L, mean ± 95% CI)	2.40 (2.29–2.49)	2.36 (2.21–2.55)	0.115
Serum phosphate (mmol/L, mean ± 95% CI)	1.11 (0.69–1.39)	1.09 (0.63–1.60)	0.700
Serum parathyroid hormone (pmol/L, mean ± 95% CI)	5.1 (1.9–12.1)	6.3 (1.4–11.5)	0.103
[†] Unpaired t-test unless otherwise specified.			
[‡] Chi-square			

Table 2
Characteristics of patients with IBD.

	Crohn's disease (n = 11)		Ulcerative colitis (n = 13)	
Montreal Classification Number of patients, n	Age at diagnosis (y)		Disease extent	
	< 17	2	Proctitis	0
	17–40	6	Left sided colitis	7
	> 40	3	Extensive colitis	6
	Location		Disease severity	
	Ileal	7	Clinical remission	0
	Colonic	2	Mild	0
	Ileocolonic	2	Moderate	8
	Upper GI	0	Severe	5
	Behavior			
	Non-stricturing, non-penetrating	4		
	Stricturing	5		
	Penetrating / fistulising	2		
	Perianal	1		
Disease activity indices	Harvey Bradshaw Index (median, range)	3 (0–8)	Simple Clinical Colitis Activity Index (median, range)	2 (0–9)
Medical therapy, Number of patients, n	Nil	0	0	
	5-ASAs only	2	1	
	Steroids ± 5-ASAs	1	3	
	Azathioprine / 6-MP ± 5-ASAs / steroids	1	3	
	Methotrexate ± 5-ASAs / steroids	0	1	
	IFX / ADA / vedolizumab ± 5-ASAs / steroids	2	2	
5ASAs, 5-aminosalicylates; 6-MP, 6-mercaptopurine; IFX, infliximab; ADA, adalimumab				

	Crohn's disease (n = 11)	Ulcerative colitis (n = 13)
	IFX / ADA / vedolizumab ± immunomodulators	53
Previous intestinal surgery / surgeries, Number of patients, n (%)	Jejunal resection	0
	Single ileo-colonic resection	30
	Multiple ileo-colonic resections	10
	Colectomy (total or subtotal)	01
5ASAs, 5-aminosalicylates; 6-MP, 6-mercaptopurine; IFX, infliximab; ADA, adalimumab		

Mean plasma haemoglobin improved similarly ($p = 0.460$) after 28 days in patients with (121 to 134 g/L) and without IBD (124 to 132 g/L).

Change in serum phosphate

Serum phosphate fell in 42 of 44 patients (95%) following FCM. The overall mean fall in serum phosphate across all patients and time periods was $0.47 \text{ mmol/L} \pm \text{SD } 0.24$ ($42 \pm 19\%$) compared with baseline. The lowest serum phosphate recorded was 0.26 mmol/L in a patient with UC at Day 7. Mean trough levels were 36% lower at Day 7, and remained lower at Day 28 compared to baseline (mean 0.95 vs 1.10 mmol/L , $p = 0.001$) (Fig. 1a). Three patients had serum phosphate below 0.6 mmol/L at Day 28. The time to nadir of serum phosphate was 2 days in 1 patient, 4 days in 8 patients, 7 days in 22 patients, 14 days in 10 patients, and 28 days in 3 patients.

Patients with CD had a significantly greater maximal reduction in serum phosphate than patients with UC (mean reduction 51% vs 32%, $p = 0.029$) (Fig. 1b).

Serum phosphate fell below 0.6 mmol/L in 24 of 44 patients (56%), similar in patients with and without IBD (Table 3).

Table 3
Number of patients and degree of hypophosphataemia noted in first 28 days
following ferric carboxymaltose (FCM)

Grade of hypophosphataemia (mmol/L)	IBD (n = 24)	Non-IBD (n = 20)
Nil or Grade 1 (≥ 0.80)	7	5
Grade 2 ($0.60 - < 0.80$)	4	4
Grade 3 ($0.30 - < 0.60$)	12	11
Grade 4 (< 0.30)	1	0

Symptomatic adverse events

Delayed adverse events were described by 11 patients with IBD (46%) and 12 without IBD (60%) (Supplementary Table 1). Fatigue, arthralgia, myalgia, headache, dyspnoea or dizziness were reported by 14 patients (6 with and 8 without IBD) in the first 7 days – these adverse events did not correlate with serum phosphate (Fig. 1c).

Change in FGF-23

Baseline iFGF-23 and cFGF-23 levels were similar in patients with and without IBD. Across all patients, iFGF-23 increased by a mean of 84% (95% CI 26–139%, $p = 0.004$), peaking within 2 days, returning to baseline at Day 28. C-terminal FGF-23 levels remained stable at day 2, but gradually declined over time, with a significant reduction at Day 28 compared with baseline levels ($p = 0.004$, paired t-test) (Fig. 1c and d).

Predictors of hypophosphataemia

Across all participants, minimum serum phosphate correlated with baseline (Pearson $r = 0.35$, $p = 0.020$) and Day 2 (Pearson $r = 0.65$, $p < 0.001$) phosphate levels (Fig. 2a and b).

In patients with IBD, there was no correlation between minimum serum phosphate and markers of inflammation (faecal calprotectin, C-reactive protein, albumin, platelet count) or baseline 25(OH)D (Fig. 2c-f).

A significant correlation between serum phosphate at Day 2 and minimum phosphate ($r = 0.67$, $p < 0.001$) was noted (Supplementary Fig. 1). Minimum serum phosphate did correlate with DBP ($r = 0.48$, $p = 0.017$) but showed a trend towards an inverse correlation with free 25(OH)D ($r = -0.39$, $p = 0.060$) and less so with bioavailable 25(di-OH)D ($r = -0.32$, $p = 0.124$).

To evaluate the effect of recurrent FCM infusions on risk of hypophosphataemia, patients who had received intravenous iron in the previous 1–2 years were analysed. Five of the 44 patients had received FCM (1 g each in 4 patients, 2 g in one patient) within the previous 12 months. Hypophosphataemia did

not occur more frequently in these patients compared to those who had not received intravenous iron over this period. One patient had received 6 g intravenous FCM in the previous 24 months. The minimum phosphate in this patient over the study period was 0.73 mmol/L, reflecting a 40% reduction from baseline.

On multiple regression analysis across all patients, baseline serum phosphate, Day 2 phosphate, C-reactive protein, 25(OH) vitamin D, 1,25(di-OH) vitamin D, were evaluated as independent risk factors for minimum serum phosphate in the follow-up period. The strongest predictor was Day 2 phosphate (β 0.577, $p < 0.001$), with baseline phosphate no longer significant (β 0.165, $p = 0.259$, adjusted R square 0.387). For patients with IBD only, a separate multiple regression model consisting of Day 2 phosphate, faecal calprotectin, DBP and free 25(OH)D was developed. Only Day 2 phosphate (β 0.533, $p = 0.052$) approached significance (adjusted R square 0.344).

When serum phosphate at Day 2 was ≥ 1.05 mmol/L, the risk of Grade 3 or 4 hypophosphataemia during follow-up was 23% compared to a 67% risk (odds ratio 7.0, 95% CI 1.6–32.0) when Day 2 phosphate was < 1.05 mmol/L.

Discussion

The risk of hypophosphataemia in patients receiving intravenous FCM is increasingly recognised; however, the risk in patients with IBD compared with patients without IBD, and associated predisposing factors, have not been previously reported. This prospective observational study demonstrated a mean phosphate reduction of 42% following FCM, similar in patients with and without IBD, with more than half the patients experiencing moderate to severe hypophosphataemia. Although patients with CD more frequently experienced hypophosphataemia than patients with UC, patients with IBD per se were not at greater risk than patients without. Importantly, neither the severity of inflammation (assessed by circulating or faecal markers) nor baseline vitamin D status predicted risk of hypophosphataemia.

Most cases of FCM-associated hypophosphataemia are asymptomatic and appear transient. Indeed, our data show that delayed adverse events secondary to FCM have no relationship with hypophosphataemia, making it difficult to recognise unless serum phosphate is measured. In the largest randomised clinical trial of patients with IBD who received FCM, mean serum phosphate was noted to fall by 38% from baseline (1.12 ± 0.22 mmol/L) to Week 2 (0.69 ± 0.24 mmol/L).[13] Hypophosphataemia as an adverse event was reported in only 6 of 244 patients in that study, and none in a follow-up maintenance study of 104 patients,[12] presumably due to most cases being asymptomatic.

Though most cases of hypophosphataemia appear transient, a minority of patients have persistent reduction in serum phosphate for at least 4–6 weeks following a single infusion of FCM. In our current study, serum phosphate remained lower at Day 28 compared to baseline (mean 0.95 vs 1.10 mmol/L, $p = 0.001$), and in 3 patients remained below 0.6 mmol/L. In another recent study, 56.9% of 52 patients receiving FCM were noted to have moderate to severe hypophosphataemia (defined in this study as $<$

0.65 mmol/L) at 2 weeks, with 13.7% of patients continuing to have serum phosphate below this level at 6 weeks.[17]

This persistent reduction in serum phosphate, particularly in the context of repeated iron infusions, may contribute to hypophosphatemic osteomalacia with fractures,[18, 23, 24] which may have delayed clinical recognition due to the non-specific nature of symptoms reported by patients and often normal plain radiography. Given that patients with IBD may have nutritional deficiencies and reduced bone density, they may be particularly susceptible to these complications.[19] Furthermore, iFGF-23 is also known to be upregulated by systemic inflammation, potentially further predisposing to hypophosphataemia.[20] Nonetheless, baseline levels of iFGF-23 were similar in patients with and without IBD in the current study. Though not performed in this study, measurement of bone turnover markers following FCM in a future study may help to stratify risk of osteomalacia in the long-term.

Eliciting risk factors for hypophosphataemia following FCM, especially in patients with IBD is, therefore, crucial, to develop potential preventative strategies. The absence of any association between systemic or intestinal inflammation, or vitamin D components (25(OH)D, 1,25(di-OH)D, free or bioavailable 25(OH)D), with risk of hypophosphataemia, means that correction of these factors may not be the answer.

Interestingly, a significant correlation between DBP and the serum phosphate nadir was noted. DBP is a liver-derived α -globulin structurally similar to albumin, which binds about 85–90% of circulating vitamin D metabolites.[25] DBP may control the availability of vitamin D metabolites, especially 25(OH)D, to tissues allowing only the small free fraction to passively enter cells through diffusion across cell membranes, or actively via interaction with membrane glycoproteins megalin and cubulin.[26] Higher concentrations of DBP may directly reduce circulating 1,25(OH)2D,[27] and so the finding of a positive correlation with serum phosphate seems counterintuitive and warrants further study.

The mechanism of hypophosphataemia following intravenous iron administration, specifically after FCM, has been investigated in numerous studies.[15, 28, 29] Consistent with previous reports, the hormone iFGF-23, which primarily inhibits renal phosphate reabsorption producing phosphate wasting but also reduces circulating 1,25(di-OH)D and thus intestinal phosphate absorption,[15, 28, 29] was demonstrated to have significantly risen by Day 2 in our study. Changes in C-terminal FGF-23 should generally be interpreted with some caution as the assay detects both cFGF-23 fragments and the intact molecule. Given that levels remained relatively stable, it is likely that impaired intracellular degradation of iFGF-23 is the likely explanation for the observed changes in FGF-23.[15]

Though patients with and without IBD did not differ in rates of hypophosphataemia, patients with CD had a higher risk of hypophosphataemia than those with UC. Subgroup analysis based upon the location of CD was not possible, since only 2 of 11 patients with CD had isolated colonic disease, with most having ileal or ileocolonic disease. Given that phosphate is absorbed in the small intestine, the difference between patients with CD and UC might be accounted for by a greater susceptibility to malabsorption of phosphate in patients with CD and requires further investigation. It is worth noting, however, that baseline phosphate was similar in patients with CD and UC ($p = 0.34$).

Ferric carboxymaltose is one of the most commonly prescribed formulations of intravenous iron worldwide, but emerging studies demonstrate a significantly higher risk of hypophosphataemia compared to other intravenous iron formulations such as iron dextran, iron isomaltoside, and ferumoxytol.[15, 17, 30] The reasons for this difference are unclear, but may be secondary to a differential effect on cleavage of iFGF23 in osteocytes by differing carbohydrate moieties.[15] Although apparently consistent, such serological effects need to be balanced against the relative clinical safety and the limited sequelae of FCM noted to date, particularly in comparison to other formulations such as iron dextran. Longer studies with more rigorous endpoints will enable a clearer distinction to be made.

The strength of this study lies in the uniform, prospective collection of data in patients with and without IBD, and its ability to clarify rates of hypophosphataemia as well as pertinent risk factors. Nonetheless, it must be acknowledged that fractional urinary phosphate excretion was not measured in patients. Previous studies have shown that an increase in phosphaturia is the primary mechanism for hypophosphataemia following intravenous iron, but whether this effect differs between patients with and without IBD, or is influenced by systemic inflammation, is an area for further study. Secondly, the duration of persistence of hypophosphataemia beyond 4–6 weeks and effect on bone turnover markers in this population remains undetermined, particularly in relation to the presence or type of IBD, and remains an avenue for further investigation.

In conclusion, hypophosphataemia following FCM occurs at similar rates in patients with and without IBD, and is not influenced by inflammation, or vitamin D status. Alternative intravenous iron formulations associated with a lower risk of hypophosphataemia might be considered for iron replacement in such patients.

Declarations

Ethics approval and consent to participate

The protocol for this study was approved by the Office of Research and Ethics at Eastern Health, Victoria, Australia (LR17-2017). Written informed consent was obtained from all participants in this study.

Consent for publication

All authors agree with the content of the manuscript and consent for its final submission.

Availability of data and materials

The authors declare that most of the data supporting the findings of this study are available within the paper. All other data are available from the corresponding author upon reasonable request.

Competing interests and funding

This work was supported by a research grant from Pharmacosmos, Denmark. Pharmacosmos had no input regarding the research or research protocol for this investigator-initiated study.

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Author contributions

Each author's contribution is as follows:

- Dr Wendy Fang: acquisition of data, analysis and interpretation of data, writing and drafting the article and its final approval;
- Ms Rachel Kenny: acquisition of data, critical appraisal of manuscript for important intellectual content, final approval of submitted version;
- Dr Qurat-Ul-Ain Rizvi: acquisition of data, critical appraisal of manuscript for important intellectual content, final approval of submitted version;
- Prof Lawrence McMahon: design of study, critical appraisal of manuscript for important intellectual content, final approval of submitted version;
- A/Prof Mayur Garg: conception and design of the study, analysis and interpretation of data, writing and drafting the article, final approval.

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References

1. Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, Macdougall IC, Rogler G, Camaschella C, Kadir R: Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. *American journal of hematology* 2017, 92(10):1068-1078.
2. Kulnigg S, Gasche C: Systematic review: managing anaemia in Crohn's disease. *Alimentary pharmacology & therapeutics* 2006, 24(11-12):1507-1523.
3. Wilson A, Reyes E, Ofman J: Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. *The American journal of medicine* 2004, 116(7):44-49.
4. Mücke V, Mücke MM, Raine T, Bettenworth D: Diagnosis and treatment of anemia in patients with inflammatory bowel disease. *Annals of gastroenterology: quarterly publication of the Hellenic*

Society of Gastroenterology 2017, 30(1):15.

5. Dignass AU, Gasche C, Bettenworth D, Birgegård G, Danese S, Gisbert JP, Gomollon F, Iqbal T, Katsanos K, Koutroubakis I: European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *Journal of Crohn's and Colitis* 2015, 9(3):211-222.
6. Ershler WB, Chen K, Reyes EB, Dubois R: Economic burden of patients with anemia in selected diseases. *Value in Health* 2005, 8(6):629-638.
7. Peyrin-Biroulet L, Lopez A, Cummings JF, Dignass A, Detlie TE, Danese S: treating-to-target for inflammatory bowel disease-associated anaemia. *Alimentary pharmacology & therapeutics* 2018, 48(6):610-617.
8. Wells CW, Lewis S, Barton JR, Corbett S: Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. *Inflammatory bowel diseases* 2006, 12(2):123-130.
9. Gasche C, Berstad A, Befrits R, Beglinger C, Dignass A, Erichsen K, Gomollon F, Hjortswang H, Koutroubakis I, Kulnigg S: Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflammatory bowel diseases* 2007, 13(12):1545-1553.
10. Garg M, Morrison G, Friedman A, Lau A, Lau D, Gibson P: A rapid infusion protocol is safe for total dose iron polymaltose: time for change. *Internal medicine journal* 2011, 41(7):548-554.
11. Kulnigg S, Stoinov S, Simanenkova V, Dudar LV, Karnafel W, Garcia LC, Sambuelli AM, D'haens G, Gasche C: A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT®) randomized controlled trial. *The American journal of gastroenterology* 2008, 103(5):1182-1192.
12. Evstatiev R, Alexeeva O, Bokemeyer B, Chohey I, Felder M, Gudehus M, Iqbal T, Khalif I, Marteau P, Stein J: Ferric carboxymaltose prevents recurrence of anemia in patients with inflammatory bowel disease. *Clinical Gastroenterology and Hepatology* 2013, 11(3):269-277.
13. Evstatiev R, Marteau P, Iqbal T, Khalif IL, Stein J, Bokemeyer B, Chohey IV, Gutzwiller FS, Riopel L, Gasche C: FERGICor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology* 2011, 141(3):846-853. e842.
14. Dahlerup JF, Jacobsen BA, van der Woude J, Bark L-Å, Thomsen LL, Lindgren S: High-dose fast infusion of parenteral iron isomaltoside is efficacious in inflammatory bowel disease patients with iron-deficiency anaemia without profound changes in phosphate or fibroblast growth factor 23. *Scandinavian journal of gastroenterology* 2016, 51(11):1332-1338.
15. Wolf M, Koch TA, Bregman DB: Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res* 2013, 28(8):1793-1803.
16. Schaefer B, Wurtinger P, Finkenstedt A, Braithwaite V, Viveiros A, Effenberger M, Sulzbacher I, Moschen A, Griesmacher A, Tilg H *et al*: Choice of High-Dose Intravenous Iron Preparation Determines Hypophosphatemia Risk. *PloS one* 2016, 11(12):e0167146.

17. Detlie TE, Lindstrom JC, Jahnsen ME, Finnes E, Zoller H, Moum B, Jahnsen J: Incidence of hypophosphatemia in patients with inflammatory bowel disease treated with ferric carboxymaltose or iron isomaltoside. *Aliment Pharmacol Ther* 2019, 50(4):397-406.
18. Fang W ML, Bloom S, Garg M: Symptomatic severe hypophosphatemia after intravenous ferric carboxymaltose. *JGH Open* 2019.
19. Garg M, Lubel J, Sparrow M, Holt S, Gibson P: Review article: vitamin D and inflammatory bowel disease–established concepts and future directions. *Alimentary pharmacology & therapeutics* 2012, 36(4):324-344.
20. David V, Francis C, Babitt JL: Ironing out the crosstalk between FGF23 and inflammation. *American Journal of Physiology-Renal Physiology* 2017, 312(1):F1-F8.
21. Smith ER, McMahon LP, Holt SG: Method-specific differences in plasma fibroblast growth factor 23 measurement using four commercial ELISAs. *Clinical chemistry and laboratory medicine* 2013, 51(10):1971-1981.
22. Health UDo, Services H: Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0 Published: May 28, 2009 (v4. 03: June 14, 2010). In.; 2016.
23. Schaefer B, Glodny B, Zoller H: Blood and Bone Loser. *Gastroenterology* 2017, 152(6):e5-e6.
24. Zoller H, Schaefer B, Glodny B: Iron-induced hypophosphatemia: an emerging complication. *Curr Opin Nephrol Hypertens* 2017, 26(4):266-275.
25. Otterbein LR, Cosio C, Graceffa P, Dominguez R: Crystal structures of the vitamin D-binding protein and its complex with actin: structural basis of the actin-scavenger system. *Proceedings of the National Academy of Sciences* 2002, 99(12):8003-8008.
26. Nykjaer A, Dragun D, Walther D, Vorum H, Jacobsen C, Herz J, Melsen F, Christensen EI, Willnow TE: An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. *Cell* 1999, 96(4):507-515.
27. Havens PL, Kiser JJ, Stephensen CB, Hazra R, Flynn PM, Wilson CM, Rutledge B, Bethel J, Pan CG, Woodhouse LR: Association of higher plasma vitamin D binding protein and lower free calcitriol levels with tenofovir disoproxil fumarate use and plasma and intracellular tenofovir pharmacokinetics: cause of a functional vitamin D deficiency? *Antimicrobial agents and chemotherapy* 2013, 57(11):5619-5628.
28. Roberts MA, Huang L, Lee D, MacGinley R, Troster SM, Kent AB, Bansal SS, Macdougall IC, McMahon LP: Effects of intravenous iron on fibroblast growth factor 23 (FGF23) in haemodialysis patients: a randomized controlled trial. *BMC Nephrol* 2016, 17(1):177.
29. Huang LL, Lee D, Troster SM, Kent AB, Roberts MA, Macdougall IC, McMahon LP: A controlled study of the effects of ferric carboxymaltose on bone and haematinic biomarkers in chronic kidney disease and pregnancy. *Nephrology Dialysis Transplantation* 2017.
30. Adkinson NF, Strauss WE, Macdougall IC, Bernard KE, Auerbach M, Kaper RF, Chertow GM, Krop JS: Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: A randomized trial. *Am J Hematol* 2018, 93(5):683-690.

Figures

Figure 1

Change in (a) serum phosphate following ferric carboxymaltose infusion in patients with and without IBD; (b) change in serum phosphate in patients with Crohn's disease and ulcerative colitis; (c) association with symptomatic adverse events; (d) change in serum iFGF-23 and (e) cFGF-23 over the study period.

Figure 2

Correlation between minimum serum phosphate during follow-up and (a) baseline and (b) Day 2 serum phosphate, across all participants; (c) faecal calprotectin, (d) C-reactive protein, (e) albumin and (f) 25(OH) vitamin D in patients with IBD.

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