Intravenous ferric carboxymaltose is associated with lowering of plasma phosphate levels in patients with gastric bypass surgery: a retrospective case series

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Summary

AIMS: Bariatric surgery induces several micronutrient deficiencies that require supplementation. For iron, parenteral infusions are usually preferred over oral supplementation. Ferric carboxymaltose infusion has been associated with hypophosphataemia, mostly transient and asymptomatic. However, in some cases, ferric carboxymaltose-induced hypophosphataemia may persist for weeks to months and may induce muscle weakness, osteomalacia and bone fractures. The aim of this study was to identify possible predictors of a clinically relevant decrease in serum phosphate after ferric carboxymaltose infusion in patients with previous Roux-en-Y gastric bypass.

METHODS: Patients with previous Roux-en-Y gastric bypass who received ferric carboxymaltose infusions between January 2018 and September 2019 and had recorded phosphataemia before and after ferric carboxymaltose infusion at the Lausanne University Hospital, Lausanne, Switzerland, were studied retrospectively. A multiple linear regression model was built with delta phosphataemia as the outcome to investigate the factors related to magnitude of serum phosphate lowering.

RESULTS: Seventy-seven patients (70 females and 7 males) with previous Roux-en-Y gastric bypass were studied. Mean age (SD) was 43.2 (10.7) years and median BMI was 30.9 kg/m² (IQR 27.9–36.4). Sixty-eight patients (86.3%) received an infusion of 500 mg ferric carboxymaltose and 9 patients (11.7%) received 250 mg ferric carboxymaltose. Forty-nine patients (63.6%) developed hypophosphataemia (<0.8 mmol/l) after ferric carboxymaltose infusion. Median plasma phosphate significantly decreased by 0.33 mmol/l (IQR 0.14–0.49) (p<0.0001). Multiple linear regression identified the ferric carboxymaltose dose as the only risk factor significantly associated with the magnitude of serum phosphate lowering, with an additional mean loss of 0.26 mmol/l with a 500 mg infusion compared to a 250 mg infusion (p = 0.020).

CONCLUSION: Ferric carboxymaltose infusions substantially decreased plasma phosphate levels in patients with previous Roux-en-Y gastric bypass. Compared to a dose of 250 mg, infusion of a dose of 500 mg ferric carboxymaltose decreased the plasma phosphate further in this population.

Introduction

Iron deficiency affects millions of people worldwide. Causes are varied and include restricted food intake, increased blood loss, increased needs or intestinal malabsorption. Patients with previous gastric bypass surgery are at risk of micronutrient malabsorption, especially iron, for which the prevalence is 16–42% [1, 2]. Given that oral absorption is reduced after Roux-en-Y gastric bypass surgery, due to decreased gastric acid secretion and bypass of the proximal small intestine, parenteral iron formulations are often preferred to enteral ones. Ferric carboxymaltose (FCM) is among the most prescribed intravenous iron preparations due to its rapid infusion rate and overall safety profile [3–5]. Despite its attractiveness, FCM was recently associated with new-onset hypophosphataemia [5–10]. Mostly underdiagnosed, hypophosphataemia after FCM infusion is usually transient and asymptomatic with a nadir about two weeks after infusion [7, 8, 11]. A prevalence of FCM-induced hypophosphataemia of up to 92% has been described when systematically sought [4, 6, 7, 11–15]. Increase of the biologically active phosphatonin fibroblast growth factor 23 (FGF23) appears to mediate hypophosphataemia induced by FCM infusion [7, 9, 10, 14, 16]. FGF23 is produced by osteoblasts in response to high levels of plasma 1,25-(OH)₂ vitamin D or of plasma phosphate. FGF23 inhibits renal reabsorption of phosphate by downregulating the tubular co-transporters NaPiIIa (SLC34A1) and NaPiIIc (SLC34A3) and by decreasing plasma levels of 1,25-(OH)₂-vitamin D. Recent reports suggest that among known iron preparations, FCM is more often linked to hypophosphataemia [5–7, 14] than ferric
Helsinki. accordance with the ethical standards of the Declaration of Helsinki. FCM carries a marked risk of hypophosphataemia. menopausal women with Roux-en-Y gastric bypass; and complications per year are commonly required, particularly in pre-
malabsorption of several micronutrients; several iron infu-
sions per year are commonly required, particularly in pre-
verse events leading to discontinuation of oral iron supple-
cation was retained in patients with an established diagno-
sin of iron deficiency by: ferritin <50 µg/l or serum ferritin ≤100 µg/l and transferrin saturation ≤30% who have failed to respond to oral iron supplementation, either be-
cause of insufficient absorption or because of digestive ad-
verse events leading to discontinuation of oral iron supple-
mentation. Phosphatemia was assessed systemically in this time period for the following reasons: Roux-en-Y gas-
tric bypass patients are at risk of poor bone health due to 
malabsorption of several micronutrients; several iron infu-
sions per year are commonly required, particularly in pre-
menopausal women with Roux-en-Y gastric bypass; and 
FCM carries a marked risk of hypophosphatemia.

**Method**

**Study design**
The study recruited patients with previous Roux-en-Y gastric bypass who received FCM infusion during their rou-
tine medical care between January 2018 and September 2019 and had plasma phosphatemia measured within 
three months before the infusion and up to one month after the infusion. In patients who had received several infusions of 
FCM with measurements of plasma phosphate levels during the study period (n = 5), the infusion that resulted in 
the lowest plasma phosphate level was arbitrarily selected.

**Participants**
The single-centre retrospective study included patients who underwent Roux-en-Y gastric bypass at Lausanne 
University Hospital, Lausanne, Switzerland. Laparoscopic Roux-en-Y gastric bypass was performed by the same sur-
tical team by creating a 15–20 ml gastric pouch, a retrocol-
ic 100–150 cm Roux alimentary limb, a 50 cm biliopancre-
atric limb, a 21 mm circular stapled gastrojejunalostomy and 
a linear stapled jejunalostomy. All patients were followed up 
for obesity at the outpatient clinic of the hospital and re-
ceived supplements (daily multivitamins, calcium and vi-
tamin D) according to Swiss guidelines on obesity and 
over, cumulative doses of iron were also associated with 
phosphatemia [8, 17]. Here, we performed a retro-
spective case series study in patients with previous Roux-
en-Y gastric bypass receiving FCM infusion, to identify 
predictive risk factors involved in plasma phosphate low-
ering. 

**Outcome**
The primary outcome was phosphatemia lowering follow-
ning a single FCM infusion up to one month after that 
infusion.

**Statistical analysis**
Standard descriptive analyses were used to summarise the 
study variables: means with standard deviations (SD) for 
approximately normally distributed continuous variables; 
medians with interquartile ranges (IQR) for continuous 
variables presenting skewness; and frequencies and per-
centages for categorical variables. A p-value <0.05 was 
considered statistically significant. To identify predictors 
of magnitude of plasma phosphate lowering, we defined 
delta phosphatemia as the outcome and examined base-
line haemoglobin, baseline ferritin, baseline eGFR, BMI, 
cumulative dose of FCM, dose of FCM and time between 
FCM infusion and post-FCM phosphatemia measurement 
as predictor variables [7, 18] using multiple linear regres-
sion. The number of covariates was chosen to respect the 
general rule for linear regression models, which is to 
include at least as many covariates as the number of study 
subjects divided by ten. Absolute risk of hypophos-
phatemia according to baseline phosphate levels was 
assessed by receiver operating characteristic (ROC) analysis. 
Outliers were defined as patients with a delta phos-
phatemia more than 3 standard deviations away from the 
mean. Outliers were kept for descriptive statistics and re-
moved for multiple linear regression model and ROC 
analysis.

**Results**
Seventy-seven patients (70 females and 7 males) with a 
mean age (SD) of 43.2 (10.7) and a median BMI of 30.9 
kg/m² (IQR 27.9-36.4) were included in the study. A de-
scription of baseline and post-FCM infusion characteristics 
is shown in table 1. Most patients (88.3%) were prescribed 
500 mg FCM at the discretion of the treating physician. A 
decrease in plasma phosphate was measured in 90.9% of 
patients within a median of 13 days (IQR 10.0–15.0) af-

**Study variables**
The anthropometric and biological parameters obtained 
from patient charts and the accredited clinical chemistry 
laboratory of Lausanne University Hospital were: age 
(years), sex (M/F), time since bariatric surgery (years), 
weight (kg), height (m) and dose of FCM (mg). Baseline 
plasma phosphate (mmol/l), ferritin (µg/l), haemoglobin 
(g/l) and calcium corrected for albumin (mmol/l) were 
measured up to three months before the accounted FCM 
infusion; eGFR (ml/min/1.73 m²) was measured up to six 
months before FCM infusion; and 25-OH-vitamin D (µg/l) 
and parathyroid hormone (ng/l) were measured up to one 
month before FCM infusion. Post-infusion plasma phos-
phate was considered until one month after FCM infusion 
and the cumulative dose of FCM was calculated up to one 
year prior the infusion considered in the study. 

The analysis was performed by the Biotistical Platfrom 
from UniSanté, using the software R (version 3.5.2) and 
GraphPad Prism (version 8.01, GraphPad Software, San 
Diego, California, United States). 

Saccharose [17], ferric isomaltoside [11, 18] or ferric dex-
tran [19]. Most of the patients did not display any symp-
toms, even though in the presence of persistent and severe 
hypophosphatemia some of them experienced bone pain, 
osteomalacia and even fractures [9, 10, 20]. Predictive fac-
tors associated with intravenous iron-induced hypophos-
phatemia have been identified, such as the type of intra-
venous iron (FCM) [7, 10, 11], low body weight [7, 8], 
high pre-perfusion haemoglobin concentration [7], normal 
eGFR [6, 7, 10] or abnormal uterine bleeding [6, 7]. More-
over, cumulative doses of iron were also associated with 
phosphatemia [8, 17]. Here, we performed a retro-
spective case series study in patients with previous Roux-
en-Y gastric bypass receiving FCM infusion, to identify 
predictive risk factors involved in plasma phosphate low-
ering.
ter FCM infusion and 63.6% of them developed new-onset hypophosphataemia; 40.8% had mild hypophosphataemia (0.6–0.8 mmol/l), 53.1% severe hypophosphataemia (0.3–0.59 mmol/l) and 6.1% critical hypophosphataemia (<0.3 mmol/l). Five patients were already mildly hypophosphataemic and one patient presented severe hypophosphataemia (0.55 mmol/l) before FCM infusion. The variation in plasma phosphate concentrations pre- and post-FCM infusion are shown in figure 1. Delta phosphataemia was found to be approximately normally distributed, except for a severe outlier in the left part of the distribution (a patient having phosphataemia increased by approximately 1.5 mmol/l). Median delta phosphataemia (IQR) was 0.33 mmol/l (0.14–0.49), with the first quartile rising to 0.17 mmol/l if the outlier is excluded. Nearly one-fifth of patients had received a cumulative dose of FCM greater than 500 mg in the year preceding the iron infusion. Mean eGFR (SD) for the whole cohort was normal at 101.5 ml/min/1.73 m² (19.2). Median ferritin level was low at 27.5 µg/l (IQR 18.3–43.8; reference range: 30–300 µg/l).

Multiple linear regression was applied to analyse the joint influence of baseline haemoglobin, baseline ferritin, baseline eGFR, BMI, cumulative dose of FCM, dose of FCM and time elapsed between FCM infusion and post-FCM phosphataemia assessment, on delta phosphataemia (outcome). An interaction between FCM dose and the time between FCM infusion and post-FCM phosphataemia was also tested and found to be not significant (not shown). The model’s assumptions (linearity, normality and homogeneity of variance) were verified by inspection of the residuals plotted against the model’s fitted values and the normal probability plot of the residuals. No evidence of assumption violation was detected. Table 2 shows the results of univariate and of multivariable regression models. Effects represent increments in mean phosphate serum lowering (mmol/l) associated with a one-point increase in continuous covariates. For the FCM dose (dichotomous variable), the effect represents the additional mean phosphate serum lowering associated with a dose of 500 mg vs a dose of 250 mg. The dose of FCM infused was significantly associated with the extent of phosphate serum lowering.

Table 1:
Characteristics of the participants and treatment. Reference range for phosphataemia: 0.8–1.4 mmol/l. Reference range for ferritin: 30–300 µg/l. Reference range for haemoglobin in women: 117–157 g/l, and in men: 133–177 g/l. Reference range for calcium corrected for albumin: 2.10–2.50 mmol/l. Reference range for 25-OH-vitamin D: 8.4–52.3 µg/l. Reference range for parathyroid hormone: 10–70 ng/l.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>43.2 (10.7)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>70 F / 7 M (90.9%/9.1%)</td>
</tr>
<tr>
<td>Time from surgery (years), mean (IQR; range)</td>
<td>4.6 (2.6–10.0; 0.4–18.5)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (IQR; range)</td>
<td>30.9 (27.9–36.4; 22.0–46.9)</td>
</tr>
<tr>
<td>Ferritin (µg/l), median (IQR; range) (n = 72)</td>
<td>27.5 (18.3–43.8; 5.0–176.0)</td>
</tr>
<tr>
<td>Haemoglobin (g/l), mean (SD) (n = 62)</td>
<td>131.0 (12.5)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²), mean (SD) (n = 66)</td>
<td>101.5 (19.2)</td>
</tr>
<tr>
<td>Calcium corrected for albumin (mmol/l), mean (SD) (n = 58)</td>
<td>2.2 (0.07)</td>
</tr>
<tr>
<td>25-OH-vitamin D (µg/l), mean (SD) (n = 39)</td>
<td>38.3 (8.0)</td>
</tr>
<tr>
<td>Parathyroid hormone (ng/l), mean (SD) (n = 35)</td>
<td>58.7 (29.7)</td>
</tr>
<tr>
<td>Pre-FCM phosphataemia (mmol/l), mean (SD)</td>
<td>1.0 (0.2)</td>
</tr>
<tr>
<td>Cumulative dose of FCM&gt;500 mg, n (%)</td>
<td>15 (19.5%)</td>
</tr>
<tr>
<td>Dose of FCM: 500 mg, n (%)</td>
<td>68 (88.3%)</td>
</tr>
<tr>
<td>Dose of FCM: 250 mg, n (%)</td>
<td>9 (11.7%)</td>
</tr>
<tr>
<td>Time between FCM infusion and post-FCM phosphataemia (days), median (IQR; range)</td>
<td>13 (10–15; 0.4–18.5)</td>
</tr>
<tr>
<td>Post-FCM phosphataemia (mmol/l), mean (SD)</td>
<td>0.7 (0.3)</td>
</tr>
<tr>
<td>Delta (pre/post infusion) phosphataemia (mmol/l), median (IQR; range)</td>
<td>0.33 (0.14–0.49; -0.29 – 1.14)</td>
</tr>
<tr>
<td>Post-FCM infusion hypophosphataemia (&lt;0.8 mmol/l), n (%)</td>
<td>49 (83.6%)</td>
</tr>
<tr>
<td>Mild (0.6–&lt;0.8 mmol/l), n (%)</td>
<td>20 (40.8%)</td>
</tr>
<tr>
<td>Severe (0.3–&lt;0.6 mmol/l), n (%)</td>
<td>26 (53.1%)</td>
</tr>
<tr>
<td>Critical (&lt;0.3 mmol/l), n (%)</td>
<td>3 (6.1%)</td>
</tr>
</tbody>
</table>

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; FCM: ferric carboxymaltose; KDIGO: Kidney Disease: Improving Global Outcomes.

* Stages of Chronic Kidney Disease according to KDIGO clinical guidelines [34]. Missing data: ferritin (n = 5); haemoglobin (n = 15); eGFR (n = 11); calcium corrected for albumin (n = 19); 25-OH-vitamin D (n = 38); parathyroid hormone (n = 42).
lowering: a higher dose (500 mg vs 250 mg) was associated with a significantly greater mean decrease in phosphataemia (difference of 0.26 mmol/l, p = 0.020). Since the choice of the FCM dose may depend on previous hypophosphataemia post-FCM, we re-estimated the model by adding baseline phosphate level as an additional covariate in the model. We found that the effect of FCM dose remained approximately the same adding baseline phosphate (0.23 mmol/l) as the one obtained in the original model (0.26 mmol/l). Thus, at equal values of baseline phosphate level, a higher dose of FCM will result in a greater drop in phosphate. The interaction between the two variables was also tested and found to be non-significant. We did not identify any other significant predictive factors but observed a trend for eGFR, specifically a protective effect of higher eGFR values on phosphate serum lowering, which can be quantified as an average reduction of 0.02 mmol/l in the phosphate lowering effect for each ten-point increase in eGFR (ml/min/1.73 m²) (p = 0.081).

ROC analysis was performed assessing baseline phosphate levels as the predictor for absolute hypophosphataemia post-FCM infusion, as shown in figure S1 and table S1 (in the appendix). Area under the curve (AUC) was 0.678. A baseline phosphataemia of ≤1.2 mmol/l (table S1) could be identified with Youden index as a risk factor for absolute hypophosphataemia after FCM infusion with a sensitivity of 94%, a specificity of 37% and a positive predictive value of 73%.

Discussion

In this retrospective case series of Roux-en-Y gastric bypass patients receiving FCM, we found that the dose of iron infused was significantly associated with the decrease in phosphate concentration. Ninety percent of the patients exhibited a decreased phosphate concentration post-iron infusion and 63.6% developed hypophosphataemia within one month after infusion. Most of the patients included were women (91%), as expected. Indeed, females are much more represented in the general gastric bypass population than males [23].

FCM-associated hypophosphataemia is frequent, mostly transient, and asymptomatic, with a nadir two weeks after the FCM infusion [7, 8, 11]. However, in some extreme cases, plasma phosphate concentration can remain low for several weeks to months and may lead to osteomalacia and bone fractures [9]. Identification of patients at risk of developing long-lasting hypophosphataemia following FCM infusion is essential for preventing major health threats.

Risk factors for hypophosphataemia have been sought in several studies [7, 18]. The type of iron infused (FCM), lower body weight, Black ethnicity, higher baseline haemoglobin levels and low baseline plasma phosphate levels have been associated with the risk of developing hypophosphataemia. Other studies identified the cumulative dose of FCM as associated with hypophosphataemia [8, 17]. The way the underlying disease may contribute to the risk of developing post-iron infusion hypophosphataemia or osteomalacia is less clear, with some case reports associated with chronic blood loss [24–26], inflammatory bowel diseases [27–29] or malnutrition [30]. In the study by Wolf et al. [7], iron deficiency due to abnormal uterine bleeding compared to unspecified iron deficiency was more often associated with post-FCM-induced hypophosphataemia. It has not been established that the dose of FCM is associated with hypophosphataemia. Wolf et al. [7] identified “lower body weight” as a risk factor and suggested that for a given dose, low body weight would expose the patient to a higher iron concentration and therefore proposed that relative dose may affect the magnitude of the plasma phosphate lowering effect. However, no study confirmed this hypothesis. Our study now demonstrates that FCM infusion dose has an impact on phosphataemia in obese patients (BMI of 30.9 kg/m²) who underwent Roux-en-Y gastric bypass surgery. We used two relatively low doses, 250 mg (about 10% of the patients) and 500 mg of FCM (90%) and showed that the higher the dose of FCM, the greater the probability of developing hypophosphataemia after infusion. This dose-dependent risk is also supported by the fact that all patients receiving FCM 250 mg were those who previously developed hypophosphataemia with FCM 500 mg. The dose effect suggests that the FCM dose should be adjusted in patients at risk. We cannot speculate on higher doses (>1000 mg) that are often encountered in clinical practice, as these high doses were not used in our clinic.

This study also found a trend between impaired renal function and a decreased risk of hypophosphataemia after FCM infusion. These results are in line with Wolf et al. [7] and are usually explained by resistance to FGF23 action seen in chronic kidney disease. Regarding other risk factors for decreased phosphataemia after FCM infusion, we did not find an association with haemoglobin or ferritin levels nor with BMI or cumulative FCM dose, as previously described. This might be due to the limited size of our cohort or to specificities due to Roux-en-Y gastric bypass.

Patients with Roux-en-Y gastric bypass are at risk of poor bone health. Chronic malabsorption of several micronu-

Table 2:
Multiple linear regression model with delta phosphataemia as outcome.

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
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<tbody>
<tr>
<td></td>
<td>Estimated effect (mmol/l)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Dose of FCM = 500 mg</td>
<td>0.258</td>
<td>0.064</td>
</tr>
<tr>
<td>Cumulative dose of FCM &gt;500 mg</td>
<td>0.055</td>
<td>-0.109</td>
</tr>
<tr>
<td>log BMI</td>
<td>-0.277</td>
<td>-0.647</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>-0.003</td>
<td>-0.009</td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.002</td>
<td>-0.006</td>
</tr>
<tr>
<td>log ferritin</td>
<td>0.026</td>
<td>-0.074</td>
</tr>
<tr>
<td>log time between FCM infusion and post-FCM phosphataemia</td>
<td>-0.001</td>
<td>-0.215</td>
</tr>
</tbody>
</table>

eGFR: estimated glomerular filtration rate; FCM: ferric carboxymaltose.
trients such as calcium and vitamin D, secondary hyperparathyroidism and lower bone mineralisation are common and increase the risk of bone fracture [31–33]. Correcting iron deficiency with the FCM formulation may add an additional risk factor for bone health by inducing hypophosphataemia and demineralisation. Schoeb et al. [13] conducted a prospective study in this at-risk population and found that almost 30% of patients with previous Roux-en-Y gastric bypass receiving a single dose of 500 mg of FCM developed hypophosphataemia. However, no bone parameters were studied. We urge clinicians to carefully investigate bone parameters in patients receiving iron infusions. We found a median delta phosphataemia of 0.33 mmol/l, similar to what Schoeb et al. found (0.3 mmol/l), but lower compared to the study by Wolf et al. (0.49 mmol/l) [7]. In the latter study, the FCM dose was three times higher (1500 mg). This is in line with the dose-response effect we observed in this study and is likely to explain the stronger effect on phosphataemia.

The weak association between low baseline phosphataemia (≤1.2 mmol/l) and post-FCM hypophosphataemia does not justify changes to clinical management and will need additional confirmatory studies.

Limitations and strengths

This study has some limitations. Firstly, it was retrospective and by definition is limited to the available data. Indeed, there were missing data for baseline ferritin (n = 5), haemoglobin (n = 15), eGRF (n = 11), calcium corrected for albumin (n = 19), 25-OH-vitamin D (n = 38) and parathyroid hormone (n = 42). However, the set of data gathered here allowed the establishment of a multiple logistic regression model with significant results, indicating sufficient power. Secondly, we did not measure FGF23 at baseline and after FCM infusion, as this parameter is recorded phosphataemia before and after FCM infusion. Thirdly, our study did not examine the symptoms of hypophosphataemia or other hard endpoints on bone or muscle strength. This should be done in future prospective studies. Fourth, females were overrepresented in our study compared to men (only 9%). However, this high proportion of women is representative of the general gastric bypass population. Fifth, we focused only on patients with previous Roux-en-Y gastric bypass with a recorded phosphataemia before and after FCM infusion. Indeed, patients without data on phosphataemia were not included. Finally, the design of our study induced a selection bias due to the selection of the lowest phosphataemia after FCM infusion for individuals who had several infusions. Due to the limited number of such cases (n = 5), a sensitivity analysis could not be performed. However, the aim of this study was not to determine the exact incidence of FCM-associated hypophosphataemia but rather to identify risk factors. The strengths of our study are the real-world context and the analysis carried out in a precisely defined population, after Roux-en-Y gastric bypass surgery, and requiring frequent iron infusions.

Conclusion

Patients with Roux-en-Y gastric bypass are at risk of iron deficiency and therefore receive repeated parenteral iron infusions, mostly FCM. We found that single doses of FCM are followed by mild to critical hypophosphataemia in this at-risk population and that the dose of FCM infused was associated with delta phosphataemia. We thus recommend monitoring plasma phosphate levels in patients with Roux-en-Y gastric bypass receiving FCM infusions or to switch to other iron formulations much less associated with hypophosphataemia, such as ferric saccharose or ferric isomaltoside.

Further studies evaluating long-term consequences of iron-induced hypophosphataemia on target organs (heart, muscles, bone, …) are warranted.

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Authors’ contribution: CPP designed the study, collected data, analysed and interpreted data, and wrote the manuscript. OB designed the study, analysed and interpreted data, and wrote the manuscript. IL performed statistical analysis, analysed and interpreted data and revised the manuscript. LF was in charge of patient care, designed the study, analysed and interpreted data and revised the manuscript. All authors read and approved the submitted version of the manuscript.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. CPP and IL declare that they have no conflict of interest. OB did receive consultancy honorarium from CSL Vifor, Switzerland. OB and LF did receive an investigator-initiated research grant from Pierre Fabre.

References


Figure S1: Receiver operating characteristic (ROC) curve of the absolute risk of hypophosphataemia as a function of baseline phosphate level. AUC: area under the curve.

Table S1:

<table>
<thead>
<tr>
<th>Cutoffs</th>
<th>Positive*</th>
<th>Negative**</th>
<th>Likelihood ratio</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>0.4–0.8</td>
<td>5</td>
<td>1</td>
<td>2.755</td>
<td>0.339–22.388</td>
</tr>
<tr>
<td>0.8–1.0</td>
<td>21</td>
<td>7</td>
<td>1.653</td>
<td>0.809–3.379</td>
</tr>
<tr>
<td>1.0–1.2***</td>
<td>20</td>
<td>9</td>
<td>1.224</td>
<td>0.651–2.302</td>
</tr>
<tr>
<td>1.2–1.4</td>
<td>2</td>
<td>8</td>
<td>0.138</td>
<td>0.0315–0.603</td>
</tr>
<tr>
<td>1.4–2.0</td>
<td>1</td>
<td>2</td>
<td>0.276</td>
<td>0.0262–2.901</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>27</td>
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</table>

Sensitivity*** 94%
Specificity*** 37%
PPV*** 73%
NPV 78%

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value.

* Disease = 1
** Disease = 0
*** A baseline phosphataemia of ≤1.2 mmol/l could be identified with Youden index as a risk factor for absolute hypophosphataemia after FCM infusion with a sensitivity of 94%, a specificity of 37%, a positive predictive value of 73% and a negative predictive value of 78%.