Reyes and Diamond., J Clin Case Rep 2017, 7:2
DOI: 10.4172/2165-7920.1000931

Journal of Clinical Case Reports

Case Report Open Access

Hypophosphataemic Rickets Due to Parenteral Ferrous Carboxymaltose in a Young Man with Crohn Disease and Iron Deficiency: A Case Report and Review of Literature

Michael Reyes* and Terrence Diamond

St. George Hospital, Australia

Abstract

We present the case of recurrent fractures and hypophosphataemic rickets that occurred in a young man who received parenteral ferrous carboxymaltose (FCM) for chronic iron deficiency associated with Crohn disease. The effect of FCM on bone and mineral metabolism and the frequency of this disorder are discussed.

Keywords: Fractures; Rickets; Crohn disease; Colectomy; Hypocalcaemia; Hypophosphataemia; Iron infusion

Case Report

A 45-year-old man was referred for bone pain and fragility fractures. He was diagnosed with Crohn disease (CD) aged 19 years and required a small bowel resection with 35 centimetres of ileum removed in 1989. His condition remained stable until 2010 when he developed colonic structuring disease requiring subtotal colectomy. An area of residual CD was left close to the anal verge due to his preference against a permanent ileostomy. He received mesalazine, varying doses of prednisolone, infliximab and azathioprine. He presented in 2015 with a four-month history of progressive bone pain involving his ribs, spine and feet. This was associated with morning stiffness and difficulty with daily activities. A rheumatologist excluded an immunological reaction to Infliximab. Examination revealed tenderness in the mid-thoracic region, left leg and metatarsophalangeal joints. A technetium bone scan revealed acute fractures over multiple ribs in an asymmetrical pattern, both pedicles of L4 vertebra, left sacral alae, femoral head, and metatarsals (Figure 1). Differential diagnoses included multiple stress fractures due to severe glucocorticoid-induced osteoporosis and malabsorption or less likely malignant bone disease.

He had no history of prior fractures. His only risk factor for osteoporosis was glucocorticoid exposure. He denied symptoms of malabsorption, but complained of malaise as a result of chronic iron deficiency. This was extensively investigated with CT abdomen, both upper and lower gastrointestinal, as well as capsule endoscopy and small bowel biopsy. He had low haemoglobin (62 g/L), serum ferritin (11 µg/L) and bone marrow iron stores, and received parenteral ferrous carboxymaltose (FCM) infusions every 8 weeks for about four years. Protein electrophoresis showed no changes and myeloma screen was negative. Thoracic spine CT and whole body PET scan excluded malignancy. Bone densitometry showed mild osteopenia (lumbar spine T-score-1.8 and femoral neck T-score-0.7). He was referred for endocrine evaluation.

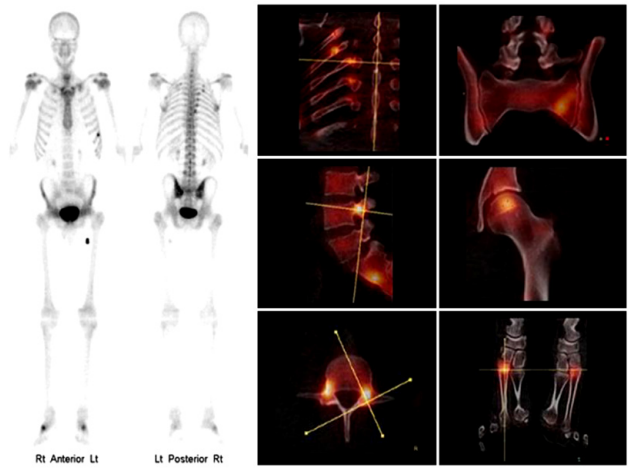

Figure 1: Technetium bone scan showing tracer uptake over multiple ribs in an asymmetrical pattern, both pedicles of L4 vertebra, left sacral alae, femoral head, and metatarsals.

He was eugonadal. The corrected serum calcium was borderline low (2.04 mmol/L). The creatinine, 25-hydroxyvitamin D (calcidiol), vitamin B12 and bone turnover markers were normal, while the parathyroid hormone (PTH) was mildly elevated (Table 1). Review of previous investigations revealed a long history of hypophosphataemia (0.21 mmol/L to 0.80 mmol/L). This was shown to be due to renal phosphate wasting as exemplified by an elevated 24-hour urine phosphate excretion and reduced renal phosphate reabsorption (TmP/GFR). Various causes for the renal phosphate loss such as primary and secondary hyperparathyroidism, 25-hydroxyvitamin D deficiency, Fanconi syndrome, and exposure to heavy metals (cadmium) were excluded. He had markedly low serum 1,25-dihydroxyvitamin D (calcitriol) and an elevated intact serum fibroblast growth factor 23 (FGF23), more than five times the upper limit of normal. Osteomalacia due to hypophosphataemia was suspected as cause for his fractures and bone biopsy was performed which demonstrated increased osteoid surfaces and osteoid thickness suggestive of a mineralisation defect (Table 1).

The hypophosphataemia, elevated FGF23, phosphaturia and reduced calcitriol were thought to be the result of the FCM exposure. His therapy was revised to parenteral iron sucrose, phosphate 500 mg TDS and calcitriol 0.25 mcg TDS. His bone pain resolved and he did not suffer further fractures. His serum phosphate, calcitriol and FGF23

***Corresponding author:** Michael Reyes, St. George Hospital, Australia, Tel: +6191131111; Fax: +61-83995178; E-mail: mikereyesmd@yahoo.com

Received January 06, 2017; **Accepted** February 04, 2017; **Published** February 08, 2017

Citation: Reyes M, Diamond T (2017) Hypophosphataemic Rickets Due to Parenteral Ferrous Carboxymaltose in a Young Man with Crohn Disease and Iron Deficiency: A Case Report and Review of Literature. J Clin Case Rep 7: 931. doi: 10.4172/2165-7920.1000931

normalised over 3 months thereby allowing the phosphate and calcitriol to be withdrawn. Figure 2 shows recovery of calcium, phosphate and TmP/GFR over time with the substitution to iron sucrose confirming the diagnosis of hypophosphataemia secondary to FCM administration.

Tests	Patient Results	Reference Range
Haematology		
Haemoglobin	87	130 g/L to 180 g/L
Iron	3	10 µmol/L to 30 µmol/L
Transferrin Saturation	5	13% to 45%
Ferritin	31	20 µg/L to 300 µg/L
Vitamin B12	250	150 pmol/L to 700 pmol/L
Biochemistry		
Creatinine	75	60 µmol/L to 110 µmol/L
ALP	71	35 U/L to 110 U/L
25-OH Vitamin D	75	50 nmol/L to 150 nmol/L
1,25-di,OH Vitamin D	**19**	60 pmol/L to 200 pmol/L
Hormone		
PTH	8.3	1.5 pmol/L to 7.6 pmol/L
Intact FGF23	289	<54 pg/ml
Testosterone	17.1	10 nmol/L to 32 nmol/L
ACTH	6.3	<11 pmol/L
Cortisol	230	120 nmol/L to 620 nmol/L
Urine Chemistry		
DPYD excretion	4.9	2.3 µmol/mmol to 5.4 µmol/mmol crea
24 hour Phosphate excretion	44	13 mmol/24h to 42 mmol/24h
Bone Histomorphometry		
Trabecular Bone Area	26.8	21% to 29%
Relative Osteoid Area	20.4	1.3% to 3.1%
Total Osteoid Surface	58.6	7.1% to 13.9%
Total Resorption Surface	5.8	2.2% to 6.7%
Osteoid Thickness	22.4	9.2 µm to 14.9 µm
Fibrous Area	0	0%

*ALP – Alkaline phosphatase, PTH – Parathyroid Hormone, ACTH – Adenocorticotropic hormone DPYD - Deoxypyridinoline

Table 1: Baseline investigations while on FCM infusion at the time of endocrine review.

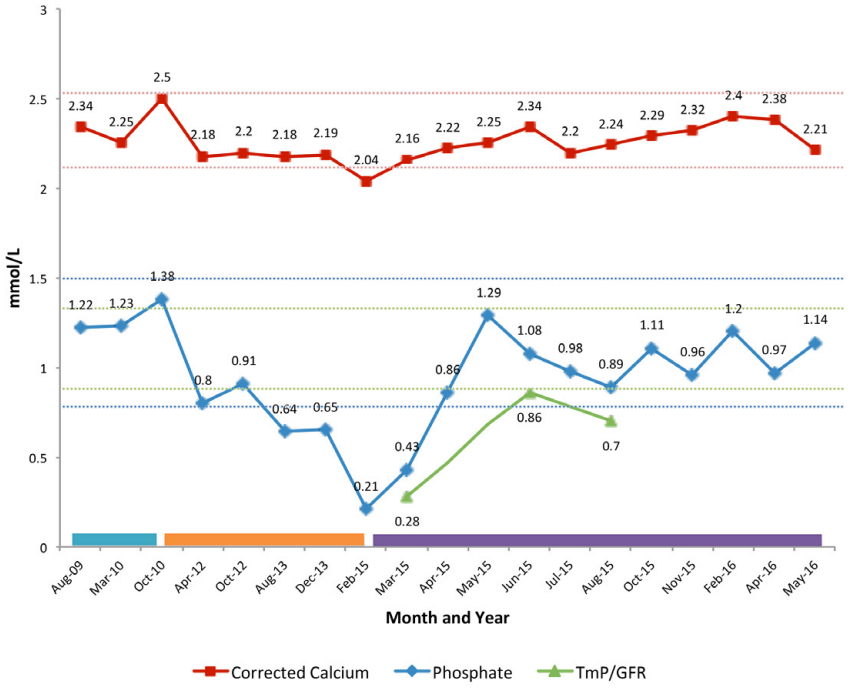

Figure 2: Corrected serum calcium, serum phosphate and renal tubular maximum reabsorption of phosphate (TmP/GFR) performed prior to and after the iron infusions. The coloured dotted lines reflect the reference range. The coloured bars indicate investigations prior to FCM infusions (■), during FCM infusions (■) and during iron sucrose infusions (■).

Discussion

Osteoporotic fractures in young men are frequently secondary to corticosteroid use, excessive alcohol consumption, hypogonadism, vitamin D deficiency, anti-convulsant medications, and hypercalciuria [1]. Non-osteoporotic fractures in young men, apart from trauma, can be due to malignancy. Our patient did not have any history of trauma, evidence of malabsorption or malignancy. He was not osteoporotic despite long-term corticosteroid use. His osteofragility fractures occurred from FCM-induced renal phosphate wasting and hypophosphataemic rickets.

Our patient suffered from chronic and poorly controlled CD. This is a common disorder with a crude annual incidence rate for CD is 17.4 per 100,000 (95% CI 13.0 to 23.2 per 100,000) [2]. It presents as bowel inflammation with loss of digestive and absorptive surface, resulting in malabsorption/ steatorrhea that can cause anaemia, hypoalbuminaemia, hypocalcaemia, hypomagnesaemia, coagulopathy, and hyperoxaluria with nephrolithiasis. Many patients need to take oral and often parenteral iron. Vertebral fractures are caused by a combination of vitamin D deficiency, hypocalcaemia, and prolonged glucocorticoid use [3].

Iron deficiency anaemia is the most common underlying condition in CD and presented a therapeutic challenge in our patient. It occurs in 36% to 90% of subjects with CD [4]. Intestinal blood loss through ulcerated mucosal surface is regarded the predominant cause of iron deficiency. Oral iron supplementation seems effective for short periods but intolerance leads to discontinuation in up to 21% [5]. Parenteral is the preferred route of iron supplementation as it is more effective, better tolerated and improves QoL to a greater extent [6]. Majority of patients will require long term recurrent iron infusions that may result in infusion related complications.

Hypophosphataemia occurs from (1) increased urinary phosphate excretion due to drugs (parenteral iron), hyperparathyroidism, vitamin D deficiency or resistance, hereditary hypophosphataemic rickets, oncogenic osteomalacia, Fanconi syndrome, and exposure to heavy metals (cadmium); (2) redistribution of phosphate from extracellular fluid into cells during diabetic ketoacidosis therapy, carbohydrate refeeding syndrome, acute respiratory alkalosis or hungry bone syndrome and (3) decreased absorption of phosphate due to inadequate intake, drugs, or chronic diarrhoea [7].

The kidney exerts a major influence on phosphate balance. Renal phosphate reabsorption occurs in the proximal tubule (60% to 70%) and in the distal tubule (10% to 15%) [7]. FGF23 is an osteocyte-derived hormone that regulates phosphate and vitamin D homeostasis. It acts in the proximal tubule to reduce renal phosphate reabsorption through the Na-Pi channel and inhibits 1-α-hydroxylase (inhibiting conversion of calcidiol to calcitriol). It also acts directly on the parathyroid to suppress PTH release [8]. Hypophosphataemia and elevated FGF23 level can be seen in hereditary hypophosphataemic rickets disorders, fibrous dysplasia, oncogenic osteomalacia [9] and following parenteral iron [10]. Our patient's investigations excluded 25-hydroxyvitamin D deficiency, malignancy and oncogenic osteomalacia. Urine 24-hour electrolyte excretion excluded Fanconi syndrome and showed isolated phosphate wasting. There was no history to suspect familial syndromes. The elevated FGF23 and low serum phosphate during FCM therapy that normalised with iron sucrose infusions are highly suggestive that his hypophosphataemic rickets was caused by the FCM therapy, inducing renal phosphate leak. The secondary hyperparathyroidism was due to the reduction in calcitriol and calcium levels and contributes to the urinary phosphate leak.

Hypophosphataemia following parenteral iron is well described and may be severe. Although the mechanism is not fully understood, recent studies suggest that reduced serum phosphate in response to FCM iron is mediated by an acute increase in FGF23, which induces phosphaturia and suppresses calcitriol, similar to genetic diseases of primary FGF23 excess [10]. Van Wyck et al. demonstrated that 70% of patients who received FCM for menorrhagia developed transient and asymptomatic reductions in serum phosphate that appeared within 2-4 weeks of treatment and resolved within 6-12 weeks [11]. Wolf et al. randomised 55 women with menorrhagia to receive parenteral FCM or iron dextran. Within 24 hours of administration, the intact and biologically active FGF23 increased and was followed by an asymptomatic reduction in serum phosphate in the FCM group as compared to the iron dextran group [12]. Hardy and Vardemergel looked at the prevalence, duration and potential consequences of hypophosphataemia after iron infusion. The prevalence of hypophosphataemia was 51% in the FCM group and 21% in the iron sucrose group that lasted up to 6 months. 13% of patients developed profound hypophosphataemia [13]. Parenteral iron complexes differ in their capability to induce unintended hypophosphataemia. Kalra and Bhandari reported iron isomaltoside to be effective in treating iron deficiency anaemia, compared to placebo, iron sucrose, and oral iron without clinically significant hypophosphataemia [6].

This case demonstrates the onset of hypophosphataemic rickets and fragility fractures in a young man with CD treated with prolonged and recurrent infusions of FCM for iron deficiency anaemia. The low phosphate levels were consequent to elevated FGF-23 levels that induced severe renal phosphate loss, reduced activation of calcidiol, decreased calcitriol level, increased PTH level, and reduced phosphate absorption. Hypophosphataemia is worse with FCM as opposed to iron sucrose, dextran, and clinically insignificant in isomaltoside. We recommend avoiding FCM infusions in treating iron deficiency associated with chronic diseases. It is imperative to monitor calciotrophic hormones during and after iron infusion so that early electrolyte replacement can be instituted as this may lessen the risk of skeletal fragility.

References

1. Ebeling PR (1998) Osteoporosis in men: New insights into aetiology, pathogenesis, prevention and management. Drugs Aging 13: 421-434.
2. Wilson J, Connell W (2010) High incidence of inflammatory bowel disease in Australia: A prospective population-based Australian incidence study. Inflamm Bowel Dis 16: 1550-1556.
3. Friedman S, Blumberg RS (2015) Inflammatory bowel disease. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J (Eds.). Harrison's Principles of Internal Medicine. (19thedn), McGraw-Hill, New York.
4. Goldberg ND (2013) Iron deficiency anaemia in patients with inflammatory bowel disease. Clin Exp Gastroenterol 6: 61-70.
5. Kulnigg S, Gasche C (2006) Systematic review: Managing anaemia in Crohn's Disease. Aliment Pharmacol Ther 24: 1507-1523.
6. Kalra PA, Bhandari S (2016) Efficacy and Safety of Iron Isomaltoside (Monofer) in the Management of Patient with Iron Deficiency Anemia. Int J of Nephrol Renovasc Dis 9: 53-64.
7. Yu ASL, Stubbs JR (2016) Causes of hypophosphatemia. Uptodate.com.
8. Lanske B, Razzaque MS (2014) Molecular interactions of FGF23 and PTH in phosphate regulation. Kidney Int 86: 1072-1074.
9. Guo YC, Yuan Q (2015) Fibroblast growth factor 23 and bone mineralisation. Int J Oral Sci 7: 8-13.
10. Schouten BJ, Hunt PJ, Livesey JH, Frampton CM, Soule SG (2009) FGF23 elevation and hypophosphataemia after intravenous iron polymaltose: A prospective study. J Clin Endocrinol Metab 94: 2332-2337.

11. Van Wyck DB, Mangione A, Morrison J, Hadley PE, Jehle JA, et al. (2009) Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: A randomized, controlled trial. Transfusion 49: 2719-2728.

12. Wolf M, Koch T, Bregman D (2013) Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. J Bone Miner Res 28: 1793-1803.

13. Hardy S, Vandemergel X (2015) Intravenous iron administration and hypophosphataemia in clinical Practice. Int J Rheumatol ID468675.