Iron Supplementation–Induced Phosphaturic Osteomalacia: FGF23 is the Culprit

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To the Editor:

We read with interest the recent article by Bartko and colleagues.1 In this article the authors report a case of hypophosphataemia and fatigue fractures occurring after iron substitution in a patient with inflammatory bowel disease. Their hypothesis is that chronic iron supplementation had induced fibroblast growth factor 23 (FGF23)-mediated phosphaturic osteomalacia, but they did not have the opportunity to confirm their hypothesis because plasma FGF23 levels were not available for their patient. We recently observed a very similar case and had the opportunity to monitor FGF23 serum levels, confirming Bartko and colleagues’1 hypothesis.

The patient was a 38-year-old man with severe Crohn’s disease, referred to our rheumatology department for pain in both hips. He received infliximab for 4 years. He also received monthly 1-g infusions of ferric carboxymaltose for 8 months for recurrent iron deficiency induced anaemia. He presented for 2 months with bilateral hip pain, with recent worsening resulting in an inability to walk. He also reported costal and sternal pain. Clinical examination revealed severe pain and limitation of both hips in every direction, but spine and sacroiliac joint examination was normal.

Biological tests showed major hypophosphataemia at 0.34 mmol/L (normal, 0.8 to 1.45 mmol/L), with a low calcium level of 1.97 mmol/L (normal, 2.20 to 2.55 mmol/L), low 25-OH-vitamin D level at 18 ng/mL (normal, 30 to 100 ng/mL), but a particularly low 1-25-OH-vitamin D level at 8 pg/mL (normal, 20 to 70 pg/mL), with normal parathyroid hormone (PTH) level at 52 ng/mL (normal, 14 to 74 ng/mL). Urine analysis showed high phosphaturia at 19.4 mmol/mmol of creatininuria with a low phosphate reabsorption rate (60%; normal >80%) and normal calcium (0.66 mmol/mmol; normal, 0.35-0.75 mmol/mmol).

MRI of the hips showed multiples fractures of both femoral heads with diffuse edema but with no sign of osteonecrosis (Fig. 1A, a and b). The bone mineral density (BMD) assessment by dual-energy X-ray absorptiometry (DXA) revealed a T-score of −2.9 SD at the femoral neck and −2.1 SD at the lumbar spine.

Serum FGF23 level was elevated at 226 ng/L (normal, 25 to 50 ng/L), leading to the diagnosis of FGF23-mediated osteomalacia. A whole-body PET scan and an octreotide scan were performed but did not identify any tumor, ruling out an oncogenic mechanism.

Administration of oral calcitriol and phosphoric acid only partially improved biological abnormalities (calcemia: 1.99 mmol/L, phosphoraemia: 0.53 mmol/L). A link to iron supplementation was then suspected, and this treatment was discontinued. The patient progressively recovered from hip, sternal, and costal pains. Routine biology reverted to normal (corrected calcemia: 2.23 mmol/L; phosphoraemia: 0.95 mmol/L; 1-25-OH-vitamin D: 82 pg/mL). Also, FGF23 serum levels returned within the normal range (36.3 ng/L) and hip MRI returned to normal (Fig. 1A, c and d).

Because of the recurrence of anemia, a new infusion of 1 g of ferric carboxymaltose was administered 2 months later in another unit. One month after this infusion, phosphate serum level again decreased (0.58 mmol/L) and FGF23 increased (59.7 ng/L; normal, 25 to 50 ng/L). The patient remained asymptomatic. All abnormalities returned to normal 2 months later and did not reoccur with oral ferrous sulfate supplementation.

Interestingly, in our case, not only phosphate but also FGF23 serum levels were monitored and we clearly observed that changes in their levels were closely linked to the timing of iron infusions (Fig. 1B).

As mentioned by Bartko and colleagues,1 cases of parenteral iron supplementation induced hypophosphataemia or osteomalacia were first described more than 20 years ago.2 It is only after the identification of FGF23 in 2000 that the possible link between such cases and this factor was pointed out.3,4

FGF23 mainly acts on the kidney and the parathyroid glands. However the exact mechanism linking iron supplementation to FGF23 remains unclear.5 Some data suggests that not iron but excipients of some parenteral preparations such as saccharose and polymaltose can mediate FGF23 upregulation.

Indeed, this association has been described with different but not all parenteral forms.6,7 In our patient, like in Bartko and colleagues’1 case, abnormalities arose with ferric carboxymaltose, resolved after discontinuation, but reappeared with reintroduction (with either carboxymaltose or sucrose). This positive re-challenge clearly confirmed the role of iron...
parenteral supplementation. Interestingly, no recurrence was observed in our patient when oral iron supplementation was later introduced. Accordingly, such effect has never been described with oral forms. Thus, in the absence of malabsorption, this administration route should be an alternative in patients requiring chronic iron supplementation. Also, the oral route might be a more accessible treatment option than the use of an anti-FGF23 antibody suggested by Bartko and colleagues. Thus, even if this new therapy seems promising for genetic FGF23-mediated phosphaturic osteomalacia, it should be reserved for nonreversible causes.

Overall, even if the main causes of FGF23-mediated phosphaturic osteomalacia and rickets are genetic or oncogenic, iatrogenic induction of FGF23-mediated phosphaturic osteomalacia should be systematically evoked in case of intravenous iron supplementation, as it is easily reversible. Effectively, even if current treatment of FGF23-mediated osteomalacia includes 1,25-dihydroxy-vitamin D and phosphate supplementation, in our case, like in the one of Bartko and colleagues, this is usually not sufficient to correct all biological parameters and etiologic treatment should be preferred. Here discontinuation of intravenous iron supplementation led to complete recovery, with FGF23 and all parameters returning within the normal range.

Disclosures

The authors state that they have no conflicts of interest.

References


