# A Man with Recurrent Fractures and Foot Pain

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## CASE DESCRIPTION

A primary care physician telephoned to inquire about the clinical significance of low alkaline phosphatase (ALP) in a 54-year-old man, which led to an investigation for the cause of the low ALP, a biochemical abnormality that is known to be underappreciated (1). The man was a military veteran currently working as a fireman. His records showed that he had a history of multiple fractures throughout his life, including the right clavicle at age 12 years, the left tibia with inflammation of the patellar ligament at the tibial tuberosity (Osgood–Schlatter disease) at 13 years, and the right ring finger when he was 15 years old. He reported severe foot pain starting in 2006 at age 44 years. At age 50 years, 2 separate radiographic examinations of the foot showed osteonecrosis of the second metatarsal (Freiberg disease) and loss of bone density. Around this time, he also reported a 2-week history of severe pain under the heel of his right foot. All these were observed despite no reported external injury or trauma. His current medications include corticosteroid nasal spray (mometasone furoate), dihydrocodeine, baclofen, cocodamol, quinine sulfate, propranolol, gabapentin, and diazepam.

As shown in Table 1, the man's records revealed that his ALP had been low on 5 separate occasions in the past 8 years. There was no biochemical evidence to suggest metabolic bone disease, hypothyroidism, or any other electrolyte disturbance, and he was vitamin D replete. Magnesium and vitamin B12 levels were marginally low, whereas zinc was within reference limits. Ferritin was raised, likely because of the acute phase response owing to fractures. Microalbuminuria was reported on 2 occasions. There was no evidence of diabetes mellitus. Given his history of fractures, we sent a plasma sample to a specialist laboratory for a vitamin B6 profile. The pyridoxal 5'-phosphate (PLP) concentration was strikingly increased for a non–vitamin B6-supplemented patient, giving a raised PLP-to-pyridoxic acid (PA) ratio (reference, <5 using SI units) (2).

| QUESTIONS TO CONSIDER |
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| • What are potential causes of low ALP activity in blood (hypophosphatasemia)? |
| • How should hypophosphatasemia be investigated? |
| • Which clinical condition is associated with hypophosphatasemia and raised PLP concentration? |

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**Table 1. Selected biochemical and hematological results.**[a]

| Analyte | Reference intervals | November 17, 2008 | July 31, 2012 | April 26, 2013 | March 13, 2014 | April 21, 2016 | June 6, 2016 | September 5, 2016 |
|---|---|---|---|---|---|---|---|---|
| ALP | 30–130 (U/L) | 12 | 15 | 15 | 15 | 7 | | |
| ALT | 5–55 (U/L) | | 22 | 28 | 19 | 51 | | |
| Total bilirubin | <1.22 mg/dL | | 0.58 | 0.70 | 0.70 | 0.70 | | |
| | (<21 μmol/L) | | (10) | (12) | (12) | (12) | | |
| Albumin | 3.5–5.0 (g/dL) | | 4.9 | 5.3 | 5.0 | 4.9 | 4.9 | 4.8 |
| Phosphate | 2.2–4.3 mg/dL | | | | | | 3.3 | |
| | (0.7–1.4 mmol/L) | | | | | | (1.05) | |
| Calcium, adjusted/ corrected | 8.8–10.4 (2.2–2.6 mmol/L) | | | | | | 10.0 (2.51) | 9.9 (2.48) |
| Vitamin D | 10–68 ng/mL | | | | | | 28.4 | 38 |
| | (25–170 nmol/L) | | | | | | (71) | (95) |
| Magnesium | 1.70–2.43 mg/dL | | | | | | 1.67 | |
| | (0.70–1.00 mol/L) | | | | | | (0.69) | |
| Zinc | 71.9–117.7mg/dL (11–18 μmol/L) | | | | | | 100 (15.3) | |
| Vitamin B12 | 197–771 ng/L | | | | | | | 196.7 |
| Folate | 9–40 ng/mL | | | | | | | 9.40 |
| Ferritin | 28–285 ng/mL | | | | | | | 309.9 |
| Hemoglobin | 13.5–18.0 g/dL | | | 16.5 | | | 16. | 15.4 |
| Glucose | 63–108 mg/dL | | | | | 97.2 | | |
| | (3.5–6.0 mmol/L) | | | | | (5.4) | | |
| Microalbumin/ creatinine | <2.5 mg/mmol (males) | | | | | 12.7 | 7.3 | |
| Vitamin B6 profile | | | | | | | | |
| PLP | 4.9–34.6 ng/mL | | | | | | | 522 |
| | (20–140 nmol/L) | | | | | | | (2112) |
| PA | 1.65–11.0 ng/mL | | | | | | | 2.2 |
| | (9–60 nmol/L) | | | | | | | (12) |
| PLP/PA ratio | <5 (using SI units) | | | | | | | 176 |

[a] Conventional units (SI units where applicable). ALT, alanine aminotransferase.

## References

1. Maman E, Borderie D, Roux C, Briot K. Absence of recognition of low alkaline phosphatase level in a tertiary care hospital. Osteoporos Int 2016;27:1251– 4.

2. Talwar D, Quasim T, McMillan DC, Kinsella J, Williamson C, O'Reilly DS. Optimisation and validation of a sensitive high-performance liquid chromatography assay for routine measurement of pyridoxal 5-phosphate in human plasma and red cells using pre column semi-carbazide derivatisation. J Chromat B Analyt Technol Biomed Life Sci 2003;792:333– 43.

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## Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the April 2018 issue of *Clinical Chemistry*. To view the case and comments online, go to http://www.clinchem.org/content/vol64/issue4 and follow the link to the Clinical Case Study and Commentaries.

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