Hypophosphatasia Could Explain Some Atypical Femur Fractures

**What we know**
Hypophosphatasia (HPP) is a rare genetic disease that affects the development of bones and teeth in children (Whyte 1985). HPP is caused by the absence or reduced amount of an enzyme called tissue-nonspecific alkaline phosphatase (TAP), also called bone-specific alkaline phosphatase (BSAP). The absence of TAP raises the level of inorganic pyrophosphate (Pi), which prevents calcium and phosphate from creating strong, mineralized bone. Without TAP, bones can become weak. In its severe form, HPP is fatal and happens in 1/100,000 births.

Because HPP is genetic, it can appear in adults as well. A recent study has identified a milder, more common form of HPP that occurs in 4 of 1000 adults (Dahir 2018). This form of HPP is usually seen in early middle aged adults who have low bone density and sometimes have stress fractures in the feet or thigh bone. Sometimes these patients lose their baby teeth early, but not always.

HPP is diagnosed by measuring blood levels of TAP and vitamin B6. An elevated vitamin B6 level [serum pyridoxal 5-phosphate (PLP)] (Whyte 1985) in a patient with a TAP level ≤40 or in the low end of normal can be diagnosed with HPP. Almost half of the adult patients with HPP in the large study had TAP >40, but in the lower end of the normal range (Dahir 2018).

**The connection between hypophosphatasia and osteoporosis**
Some people who have stress fractures get a bone density test and are treated with an osteoporosis medicine if their bone density results are low. The first line osteoporosis medicine is a bisphosphonate (BP) like Fosamax, Actonel, Boniva, and Reclast. These medicines work by slowing the breakdown of bone. In most patients, they effectively reduce the risk of fractures. However, because BPs are analogs (mimics) of Pi, which is elevated in HPP, patients with HPP should not be treated with a BP.

**The connection between hypophosphatasia and atypical femur fractures**
Atypical femur fractures (AFFs) have been associated with long-term use of BPs since they were first observed in 2007 (Goh 2007). Despite how rare AFFs are compared to the ability of BPs to prevent hip fractures and vertebral fractures, patients have become frightened about the risk of AFF. Because of this fear, there has been a substantial decline in the use of BPs and, in turn, we are now seeing an increase in the rate of hip fractures in the US.

There is now a possible explanation for AFFs. They could be happening in patients who have undiagnosed HPP and received the wrong fracture prevention medicine.

**What You Can Do**
Before deciding on a medicine for osteoporosis, talk with your doctor about the best choice available by learning more about your particular skeletal health.

©2018 American Bone Health
1. Ask your doctor to review your total alkaline phosphatase (TAP) and obtain a vitamin B6 level [serum pyridoxal 5-phosphate (PLP)] if your TAP is in the lower end of the normal range (40-60) or is below 40, to rule out HPP. If your B6 level is elevated, you may have HPP, and you would be a candidate for Strensiq®, Tymlos® or Forteo® - but not a BP or Prolia®.

2. Ask your doctor about the rate of your bone turnover. These tests might include a CTx, NTx, BSAP or P1NP. If you have a low rate of bone formation (low BSAP or P1NP) and have an elevated risk of fracture, you would be a candidate for Tymlos® or Forteo® - but not a BP or Prolia®.

3. After your bone density test, calculate your fracture risk using the ABH FORE Fracture Risk Calculator https://americanbonehealth.org/calculator/ or FRAX® Fracture Risk Assessment Tool https://www.sheffield.ac.uk/FRAX/ if you have low bone density, but are at low fracture risk, you are not a candidate for an osteoporosis medicine. You do need to make sure to take preventive steps to reduce further bone loss. https://americanbonehealth.org/what-you-should-know/bone-healthy-goals/

4. There is a new medicine to treat HPP called Strensiq® (asfotase alfa); but patients who are not candidates for that medicine may be prescribed either Tymlos® (abaloparatide) or Forteo® (teriparatide) for their osteoporosis.