COULD YOUR PATIENT'S

DIFFUSE MUSCULOSKELETAL PAIN
JOINT PAIN

CPPD DISEASE/PSEUDOGOUT
CHONDROCALCINOSIS
CALCIFIC PERIARTHRITIS

OSTEOPENIA
OSTEOPOROSIS
OSTEOMALACIA

BONE PAIN

BE CAUSED BY **HYPOPHOSPHATASIA**?[1-3]

Meet Jake, a 51-yo male referred for acute pseudogout flare[5,a]

History of Presenting Illness

Jake is referred from his PCP's office for acute worsening of chronic knee pain. He has a history of pseudogout and describes this as similar to previous flares.

Past Medical History

- History of ambulation difficulties due to knee pain
  - Diagnosed with pseudogout at age 44
- Poor dentition

Exam

- General: moderate discomfort apparent
- Right knee: swollen, warm, and erythematous

Studies and Labs

- Knee aspirate: CPPD crystals
- X-ray right knee: diffuse chondrocalcinosis

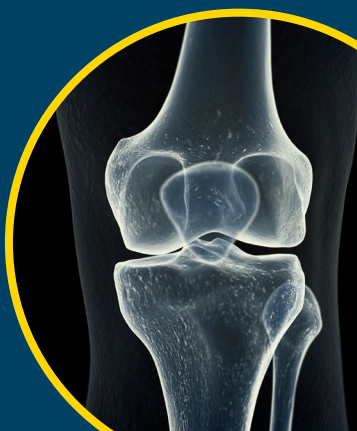
Low ALP activity disrupts calcium and phosphate metabolism and can cause CPPD crystal deposition[3]

Why consider HPP for Jake?[2]

- ☑ Signs/symptoms
  - CPPD disease/pseudogout
  - Chondrocalcinosis
  - Poor dentition
- ☐ Low ALP
  - **Jake's labs should be assessed to determine if he has low ALP and to rule out other causes of CPPD**

Remember the "4 *H*'s" for metabolic causes of CPPD[11]

- Hypomagnesemia
- Hyperparathyroidism
- Hemochromatosis
- Hypophosphatasia



Meet Stella, a 34-yo female referred for chronic lower extremity pain and weakness[4]

History of Presenting Illness

Stella is referred for a 10-year history of diffuse lower extremity bone pain and myalgias. Two years ago, she also developed mild proximal lower extremity weakness. Her symptoms are worse with physically demanding activities and in cold weather.

Past Medical History

- Chronic lower extremity bone pain, myalgias, and weakness
- Premature delivery at 30 weeks
- Recurrent dental caries

Exam

- General: short stature
- Gait: difficulty climbing stairs, waddling gait
- Lower Extremity Exam
  - Bilateral proximal lower extremity weakness (4/5) with difficulty getting off floor
  - Normal reflexes
  - No tenderness

Studies and Labs

- X-ray feet: short metatarsals
- X-ray hip: acetabular dysplasia
- Cortical osteoporosis
- Labs
  - ALP: 28 U/L
  - All other serum, urinary, and immunologic analyses were normal

Low ALP is the biochemical hallmark of HPP[2]

Why consider HPP for Stella?[2]

- Signs/symptoms
  - Diffuse musculoskeletal pain
  - Osteoporosis
  - Short stature and history of dental abnormalities
- Low ALP
  - If **other causes** of low ALP are ruled out, the diagnosis of HPP can be made based on signs/symptoms + low ALP

Avoid ineffective and potentially harmful management[1,2,6,7]

Ensuring a correct diagnosis for Stella will avoid ineffective and potentially harmful management

Bisphosphonates
may worsen skeletal hypomineralization in HPP

High-dose vitamin D and calcium
may exacerbate hypercalcemia and hypercalciuria in HPP

RANKL inhibitors
do not address the underlying cause of HPP

In hypophosphatasia, low ALP enzyme activity leads to poor bone quality and the accumulation of substrates, resulting in an array of multisystemic consequences[1,2]

- In HPP, loss-of-function mutations in the *ALPL* gene result in deficient tissue-nonspecific alkaline phosphatase enzyme activity
- Low ALP enzyme activity impairs bone formation, diminishing bone strength and quality, while PPi and Ca^{2+} accumulate throughout the body
  - PPi is an inhibitor of hydroxyapatite and bone mineralization, and its accumulation contributes to defective bone mineralization in HPP

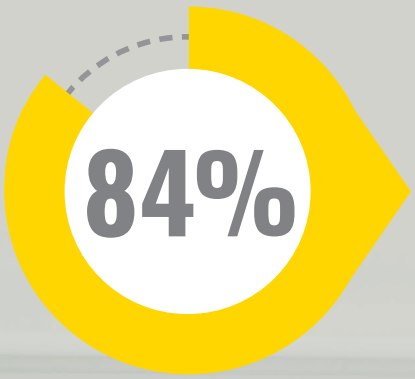
When considering a diagnosis of HPP, rule out secondary causes of low ALP, including[8-10]

- Certain medications
- Large blood transfusions
- Improper blood collection
- Profound hypothyroidism
- Celiac disease
- Severe malnutrition
- Pernicious anemia
- Wilson disease
- Multiple myeloma
- Magnesium, vitamin C, or zinc deficiency

NOTE: Not an all-inclusive list.

CHECK ALP

ACCORDING TO A 2019 REPORT FROM A GLOBAL REGISTRY,



Including:

- Calcific periarthritis (7%)
- Chondrocalcinosis (4%)
- Fibromyalgia (10%)
- Pain[b] (75%)
- Pseudogout (6%)

OF 137 ADULT PATIENTS WITH HPP HAVE A HISTORY OF RHEUMATIC SYMPTOMS[12,c]

IN A STUDY OF HOSPITALIZED ADULT PATIENTS WITH MULTIPLE ALP ASSESSMENTS, ¼ OF PATIENTS WITH PERSISTENTLY LOW ALP (**<40 U/L**) WERE ON THE RHEUMATOLOGY SERVICE[13]

THINK OF **HPP**

[a]Case developed from composite data from a survey of case reports; [b]Combines generalized body pain, chronic bone pain, and chronic muscle pain; [c]Adult patients with evaluable data.

Abbreviations: ALP, alkaline phosphatase; Ca, calcium; CPPD, calcium pyrophosphate dihydrate; DXA, dual-energy X-ray absorptiometry; HPP, hypophosphatasia; PCP, primary care physician; PPi, inorganic pyrophosphate; PRN, pro re nata, as needed; yo, -year-old; RANKL, receptor activator of nuclear factor-kappa B ligand.

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ALEXION®