Objectives:

- To present a patient with hypophosphatasemia (HPP) (below normal serum alkaline phosphatase) who was referred to the osteoporosis clinic due to low bone mineral density.
- To discuss the significance of adult hypophosphatasia as differential diagnosis in cases of low mineral bone density and low alkaline phosphatase activity.

Case: 52-year-old Caucasian, postmenopausal woman with history of interstitial cystitis, migraines, diverticulosis, arthritis, irritable bowel syndrome and a remote history of anorexia in her early teens was referred to the osteoporosis clinic for evaluation of the persistent low bone mineral density. She also had history of ovary-sparing hysterectomy at the age of 40 for dysfunctional bleeding. She was diagnosed with osteopenia at age of 46 and was started on an oral bisphosphonate. She reported poor compliance in taking this medication. She stopped taking the bisphosphonate after a couple years (patient unable to recall full duration). She is currently taking oral progesterone and estrogen supplements prescribed by her gynecologist for the past 2 years. She has family history of osteoporosis in her mother. Her BMI 19.35 and rest of the exam is within normal limits.

Laboratory studies are significant for Calcium 9.1 mg/dl (normal 8.4-10.2), Phosphorus 4.4 mg/dl (normal 2.4-5), Magnesium 2.2mg/dl (normal 1.8-2.5), Creatinine 0.9mg/dl (normal 0.4-1.2), PTH 57.1 pg/mL (normal 12-90), TSH 1.981 mcIntUnits/mL (normal 0.35-5.5), 25-OH Vitamin D 26 (normal 30-100), Alkaline phosphatase 28 units/L (normal 39-117), T. bili 0.6 mg/dL (normal 0.4-1.4), AST 17 units/L (normal 14-40), ALT 13 units/L (normal 10-44), Immunofluorescent Electrophoresis and serum light chains were normal, Urine NTX 42 (normal 4-64), urine spot calcium/creatinine normal, Anti Tissue Transglutaminase < 5 units (normal ≤ 19). DEXA scan from a year before showed L1-L3 T-score -0.9 and Z-score 0.1, Left hip with femoral neck T-score -3.0, Z-score -1.7 and Total hip T-score -2.7, Z-score -1.9. Subsequent testing showed Copper 93mcg/dL (normal 70-175), Thiamine 26 mMol/L (normal 8-30), Vitamin B6 39.4 ng/mL (normal 2.1-21.7). Patient was not taking multivitamins at the time of testing for Vitamin B6. A CT of the abdomen was performed for abdominal pain showed incidental bilateral adrenal gland hyperplasia; overnight Dexamethasone suppression testing was normal. Patient’s alkaline phosphatase has been ranged between 26-37 units/L for the last 5 years. DEXA scan repeated 2 years from the last scan showed L1-L3 T-score -0.9 (vs. previous -2.3%), left hip femur neck T-score -3.0 (vs. previous -9.4%), left hip total T-score -2.7 (versus previous -4.1%).

Discussion: Our patient presented with low bone mineral density. Her initial evaluation was significant for Vitamin D deficiency and low alkaline phosphatase. She received vitamin D replacement and continued the hormonal therapy. We initially thought the low alkaline phosphatase could be due to prior exposure to bisphosphonates. Other etiologies for low alkaline phosphatase, including anorexia, vitamin D toxicity, Celiac disease, Wilson’s disease, multiple myeloma, and Vitamin B12 deficiency, were ruled out. With strong suspicion for adult HPP, pyridoxal phosphate level (PPI) was checked, a substrate for tissue non-specific alkaline phosphatase enzyme (TNSALP), and was found to be elevated. Genetic study to look for defective TNSALP allele is considered but could not be performed at this point due to the cost.

Hypophosphatasia is an inborn-error with either an autosomal recessive or autosomal dominant transmission characterized by low alkaline phosphatase level secondary to a mutation in ALPL gene on chromosome 1. Reduced or absent TNSALP activity results in extracellular accumulation of PPI, which is a potent inhibitor of bone mineralization. The presentation is quite variable, ranging from birth to adulthood with worse prognosis if presented early. Adult HPP are at risk for fractures and increased orthopedic surgeries. They can also present with dentition abnormalities, calcified arthritis or Calcium pyrophosphate deposition disease (CPPD). Bisphosphonates are structural analogues of PPI and can lead to atypical sub trochanteric femoral fractures. Teriparatide has been used to treat fractures in patients with HPP.

Conclusion: Adult Hypophosphatasia should be considered in patients with persistent hypophosphatasemia, even in asymptomatic patients. Low bone mineral density should be carefully evaluated in these patients as diagnosis and treatment is challenging.