An audit of the incidence and causes of low serum alkaline phosphatase (ALP).

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INTRODUCTION

- It is well known that low alkaline phosphatase (ALP) concentrations remain unnoticed and are rarely followed up clinically.[1] The prevalence of a low ALP in the general population remains largely unknown with one estimate stating an incidence of 0.19%.[2]
- After excluding artefactual causes, the most common causes of low ALP are malnutrition, low zinc and/or magnesium and less commonly due to a familial condition known as **hypophosphatasia (HPP)**. Low ALP is also observed in several conditions, but the mechanistic basis of these associations remain unknown (see Table 1).
- **HPP**:
  - is caused by a loss-of-function mutations causing deficiency of tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP)[3].
  - It is an autosomal dominant (and in some forms a recessive) disorder with more than 300 known variants.
  - The incidence is: 1:300,000 (severe form); 1:6370 Europeans; incidence of milder presentations remain unknown.
  - It is characterised by defective bone mineralization leading to skeletal & dental abnormalities and systemic complications.
  - It is diagnosed by measuring vitamin B6 (pyridoxal-5 phosphate, PLP) where it is high because the low concentration or absence of ALP results in decreased hydrolysis and hence accumulation of the substrate. Individuals are functionally deficient as there is poor uptake into tissues such as the central nervous system resulting in pyridoxine-dependent seizures.
  - It presents at all ages: perinatal (~100% mortality); infantile (73% mortality at 5y); childhood (tooth loss; rachitic); adulthood (usually in middle-age).
  - HPP carries considerable morbidity and yet remains largely undetected in affected individuals. It is often misdiagnosed as osteoporosis. The treatment given, which is bisphosphonates is contraindicated in HPP where it exacerbates fracture risk.
- The aim of this audit was to determine the incidence of low ALP in our local hospital with the view to delineate the potential causes and develop pragmatic solutions to identify individuals affected by HPP.

Table 1. CAUSES OF LOW ALP (associated mechanism)

GENERAL CAUSES
Improperly collected blood – EDTA contamination (cofactor chelation)
Inappropriate reference range (assay-dependent; age- and gender-based)
Medications: clofibrate, chemotherapy, glucocorticoids, bone anti-resorptives, antacids (milk-alkali syndrome)
Massive blood transfusion (haemodilution)
BIOCHEMICAL CAUSES
Malnutrition (reduced cofactor supply)
Magnesium deficiency (cofactor)
Zinc deficiency (cofactor)
Hypothyroidism
Vitamin D intoxication
Vitamin C deficiency
Hypophosphatasia (mutation in TNSALP gene)
DISEASE ASSOCIATIONS
Bone diseases: osteogenesis imperfecta, achondroplasia
Cardiac bypass surgery (massive blood transfusion)
Pernicious or severe anaemia
Wilson disease (Cu^{2+} competes with Zn^{2+}; free-radical damage generated by Cu^{2+})
Cushing syndrome
Multiple myeloma
Coeliac disease
Radioactive heavy metal poisoning

METHOD

- Following local approval**,** all low ALP results defined pragmatically as less than 30 U/L with corresponding vitamin B6 (pyridoxal-5 phosphate, PLP), magnesium, zinc, calcium and phosphate results were gathered from our local database over the period July 2023-July 2025.
- We also searched the electronic patient records for relevant clinical information.
- Over the study period we identified 2187 cases of low ALP, which was 0.4% of the total ALP tested over the period.
- We aimed to determine how many cases were attributable to the commonly available tests, magnesium and zinc and the definite test for diagnosis, which is PLP (vitamin B6).
- We also aimed to determine the typical presenting symptoms by reviewing the patient records when a diagnosis of HPP was made.

RESULTS

AUDIT QUESTION	FINDING
Cases of low ALP over the period of study (percentage of total requests)	2187 (0.4%)
Proportion with low magnesium	91 (4.2%)
Proportion with low zinc	8 (0.4%)
Proportion with high vitamin B6	14 (0.6%)

Case records of patients with a presumptive diagnosis of HPP n=14
2 patients on bisphosphonates, a contraindicated medication in this condition.
4 patients were on vitamin D supplementation, which is not recommended in this condition.
4 presented with fractures, 3 of those patients had recurrent fractures.
6 had joint-related conditions such as chondrocalcinosis and osteoarthritis.
4 had neurological conditions such as sciatica.
4 had gastroenterological issues such as inflammatory bowel disease (IBD).

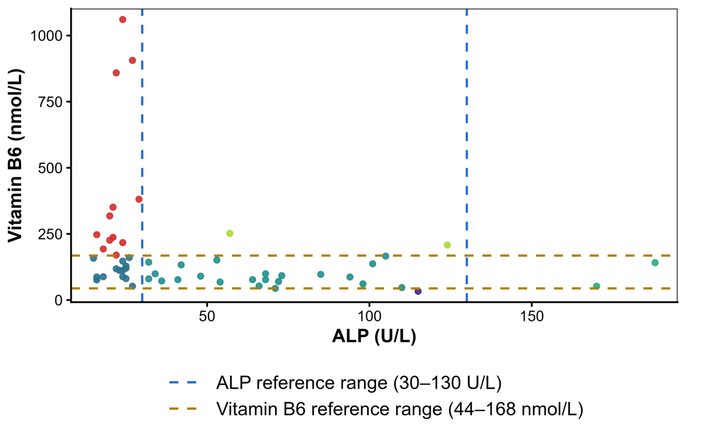


Figure 1. Relationship between low ALP and vitamin B6. Note the high proportion of high vitamin B6 in individuals with ALP below the reference limit.

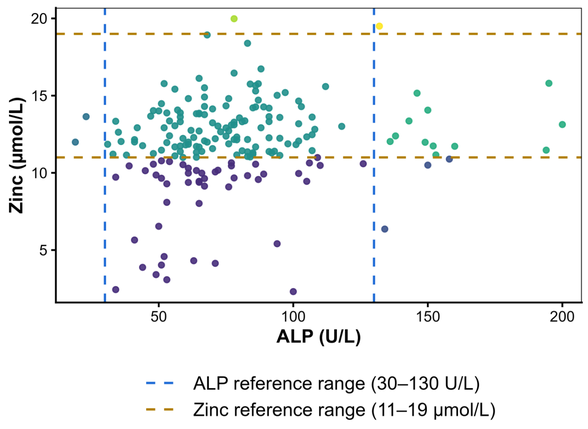


Figure 2. Relationship between low ALP and zinc.

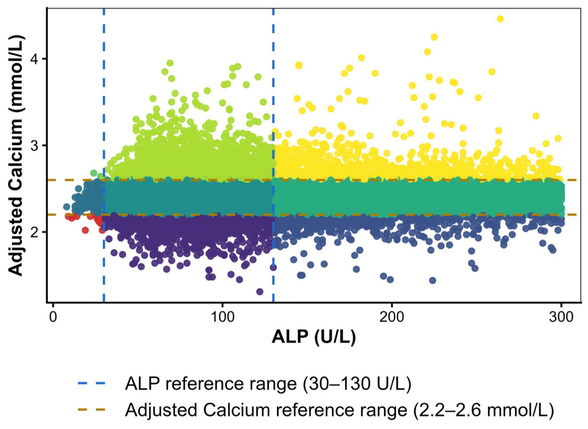


Figure 3. Relationship between low ALP and adjusted calcium.

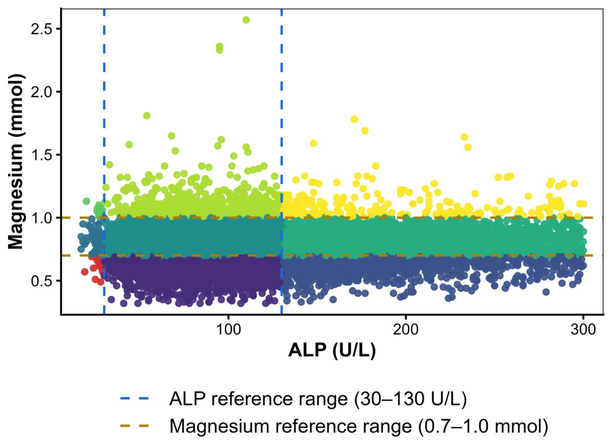


Figure 4. Relationship between low ALP and magnesium.

KEY FINDINGS

- The incidence of hypophosphatasaemia in our population is 4 in 1000 persons.
- The prevalence of hypophosphatasia (HPP) in our population is 6 in 1000 persons.
- The incidence of mild forms of HPP remains unknown and based on our preliminary findings it might be higher than previously reported.
- Low magnesium was the most common cause of a low ALP (4.2%) in our population.
- There was no significant correlation between ALP and vitamin B6, zinc, adjusted calcium or phosphate in our study population (figures 1-4)
- A low ALP with typical clinical findings resulted in higher concentrations of vitamin B6 (figure 1)
- The overall reference range in our study population was largely concordant with the CALIPER reference ranges (figure 5) suggesting that there was minimal ascertainment bias.

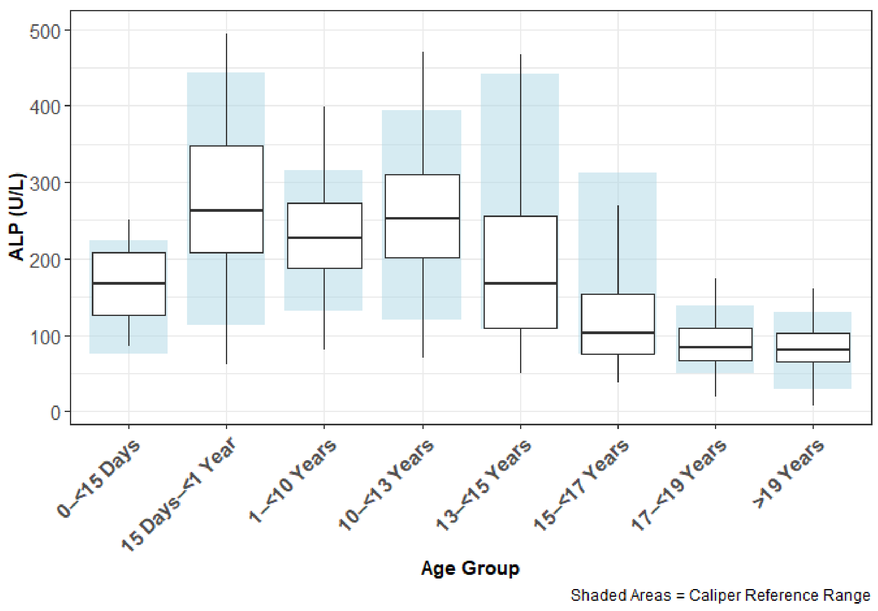
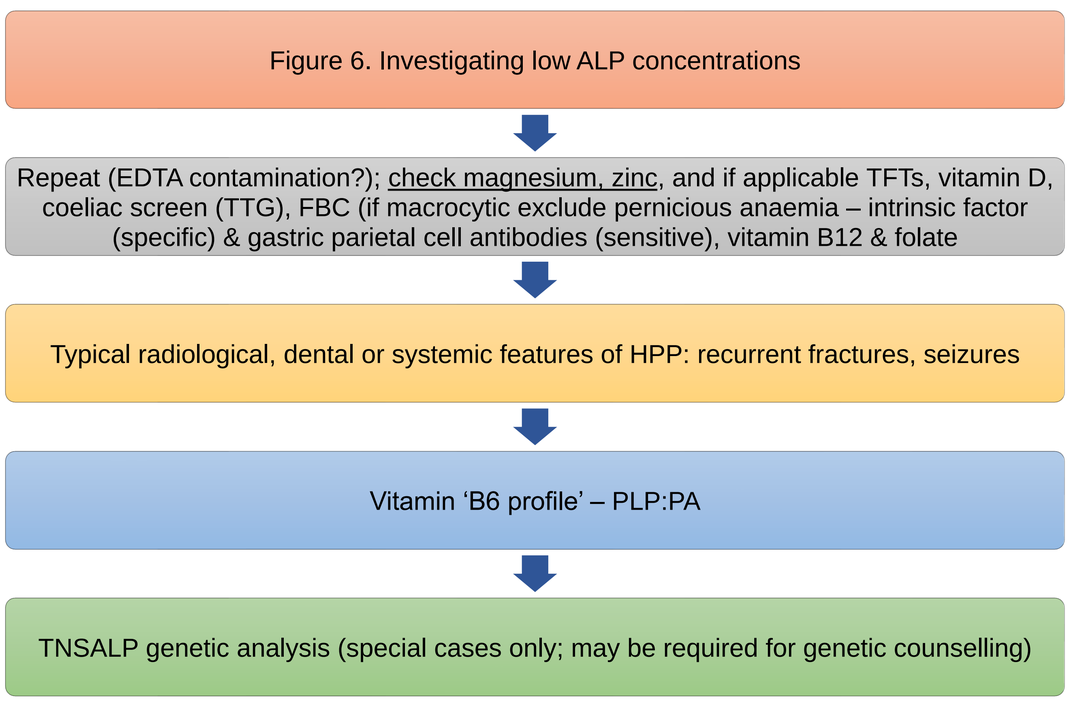


Figure 5. The distribution of ALP in our population by age group. The blue-shaded region is the Caliper reference range for the analyser in use – Beckman AU.



KEY POINTS

- Low serum ALP is underappreciated and mostly overlooked. Assay-dependent and age- and sex-specific reference intervals should be used.
- We recommend that low ALP results are flagged in laboratory information systems.
- Exclude causes such as malnutrition, magnesium and zinc deficiency, and correlate biochemical findings with clinical features. See Figure 2.
- A rare cause of hypophosphatasaemia is HPP, a diagnosis that is known to be easily missed. HPP presents at any age, but in the adult-onset form it usually presents in middle age.
- The first-line test for HPP is low serum ALP. To confirm HPP, measure the vitamin B6 profile—raised PLP level is a sensitive and specific marker of HPP .
- In those with HPP, treatment with bisphosphonates increases fracture risk and is contraindicated. Vitamin D at pharmacological doses and/or calcium supplementation may induce or aggravate hypercalcemia.
- We suggest implementing a reflex testing protocol for low ALP to include zinc, magnesium and vitamin B6, together with a referral pathway for the patient. This might need to be dependent on clinical presentation.

REFERENCES

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3. Whyte MP. Hypophosphatasia—aetiology, nosology, pathogenesis, diagnosis and treatment. Nat Rev Endocrinol 2016;12:233– 46.