Osteoporosis International (2023) 34:327–337
https://doi.org/10.1007/s00198-022-06597-3

ORIGINAL ARTICLE

A low serum alkaline phosphatase may signal hypophosphatasia in osteoporosis clinic patients

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Received: 31 August 2022 / Accepted: 3 November 2022 / Published online: 24 November 2022

Abstract

Summary Low serum alkaline phosphatase (ALP) was found in 9% of patients attending an osteoporosis clinic, 0.6% of hospital patients, and 2/22 with an atypical femoral fracture. Hypophosphatasia was diagnosed in 3% of osteoporosis clinic patients with low ALP. Low ALP is a screening tool for hypophosphatasia, a condition potentially aggravated by antiresorptive therapy.

Introduction Hypophosphatasia (HPP) is an inherited disorder associated with impaired primary mineralisation of osteoid (osteomalacia). HPP may be misdiagnosed as osteoporosis, a reduction in the volume of normally mineralized bone. Both illnesses may result in fragility fractures, although stress and atypical fractures are more common in HPP. Antiresorptive therapy, first-line treatment for osteoporosis, is relatively contraindicated in HPP. Misdiagnosis and mistreatment can be avoided by recognising a low serum alkaline phosphatase (ALP). Our aim was to determine the prevalence of a low ALP (< 30 IU/L) in patients attending an osteoporosis clinic, in a hospital-wide setting, and in a group of patients with atypical femoral fractures (AFF).

Methods This was a retrospective study of patients attending an osteoporosis clinic at a tertiary hospital during 8 years (2012–2020). Patients were categorised into those with a transiently low ALP, those with low ALP on ≥ 2 occasions but not the majority of measurements, and those with a persistently low ALP. ALP levels were also assessed in hospital-wide records and a group of patients with AFF.

Results Of 1839 patients attending an osteoporosis clinic, 168 (9%) had ≥ 1 low ALP, 50 (2.7%) had low ALP for ≥ 2 months, and seven (0.4%) had persistently low ALP levels. HPP was diagnosed in five patients, four of whom had persistently low ALP levels. The prevalence of HPP was 0.3% in the osteoporosis clinic and 3% in patients with ≥ 1 low ALP. Low ALP occurred in 0.6% of all hospital patients and 2/22 with AFF.

Conclusion Persistently low ALP in osteoporosis clinic attendees is easy to identify and signals the possibility of hypophosphatasia, a condition that may be mistaken for osteoporosis and incorrectly treated with antiresorptive therapy.

Keywords Alkaline phosphatase · Bisphosphonate · Hypophosphatasemia · Hypophosphatasia · Osteoporosis

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Introduction

Osteoporosis is a public health issue due to the significant morbidity and economic burden resulting from fragility fractures [1]. Fracture liaison services and osteoporosis clinics are committed to management of patients with bone fragility. The majority of referred patients have sustained fragility fractures or have low bone mineral density (BMD) [2]. Many diseases may account for bone fragility or reduced BMD including primary hyperparathyroidism, malabsorption, cortisol excess, mastocytosis, and others, making a diagnosis challenging [2, 3]. One rare illness causing secondary osteoporosis is hypophosphatasia (HPP) which may present with fragility, stress, or atypical fractures.

HPP is an inborn error of metabolism inherited in an autosomal dominant or recessive pattern with incomplete penetrance [4, 5]. A loss-of-function mutation within the gene *ALPL* (alkaline phosphatase liver/bone/kidney isoenzyme [6]) encoding tissue non-specific alkaline phosphatase (TNSALP) impairs hydrolysis of inorganic pyrophosphate, an inhibitor of mineralisation [5]. The mutation results in reduced serum ALP activity and accumulation of inorganic pyrophosphate (PPi), pyridoxal-5′-phosphate (PLP) and phosphoethanolamine [7]. Hence, TNSALP plays a role in vitamin B6 metabolism, with deficiency resulting in high vitamin B6 levels and associated neurological symptoms [7].

Diagnosis of HPP is based on clinical suspicion, laboratory testing, and DNA sequencing, although the latter is not always required. Over 400 defects in TNSALP have been identified with varying presentations relating to the degree of residual ALP activity [7, 8]. HPP can manifest at any age with varying severity [9]. Adults may suffer from stress or fragility fractures with impaired healing. Consequently, misdiagnosis as age-related osteoporosis may occur. Subsequent treatment with bisphosphonates, analogues of pyrophosphate, may exacerbate the inhibitory effect of this accumulated substrate on primary mineralisation. Atypical femoral fractures (AFF) may be the result of HPP [10] and may also be a rare adverse effect of antiresorptive therapy [11].

Finding low ALP may signal the possible diagnosis of HPP [12]. Screening patients for low ALP in an osteoporosis clinic assists in identification of HPP and avoidance of mistreatment with antiresorptive therapy which may aggravate the risk of AFF. This study was undertaken to determine the prevalence of low ALP levels in patients presenting to an osteoporosis clinic, in a whole hospital setting and in patients with AFF.

Methods

This study was performed at The Alfred Hospital, an adult tertiary institution which services a wide catchment area and a large group of lung and heart transplant recipients. Medical records of all adult patients seen in The Alfred Osteoporosis Clinic from its inception in April 2012 until April 2020 were reviewed. Pathology results from January 2008 to April 2020 were accessed and ALP levels reviewed. The electronic medical record was interrogated in all patients with at least one ALP level below 30 IU/L, the lower limit of the reference range in Australia [13].

All ALP levels for each patient were collated to assess the proportion of low levels over time as there was concern that evaluation of the median ALP level alone might misrepresent the individual's true ALP value. Patients with at least one low ALP were categorised into three groups. Group 1 comprised those with transiently low ALP levels, defined as a low ALP during only one month out of all the months where this was measured. Group 2 comprised those with low ALP during at least two months, but the majority of their measured ALP levels were normal (> 30 IU/L in over half the months when the ALP level was assessed). Group 3 comprised those with a persistently low ALP, defined as a low ALP level in over half of the months when measured. This categorisation was used to minimise over-investigating those with transient periods of low ALP values (when multiple tests were done in short time periods) while not missing recurrent low ALP values in those with fewer pathology tests.

Medical records were reviewed to identify circumstances around low ALP levels in all patients with a low ALP. This included lung and/or cardiac transplantation involving cardiac bypass, plasma exchange, intravenous immunoglobulin, high-dose immunosuppression, surgery, sepsis, chemotherapy, haemorrhage, or bone marrow transplant (Fig. 2). Data collection included previous fragility fractures, AFFs, musculoskeletal pain, dental abnormalities, history of childhood rickets, and family history of osteoporosis. Fractures were recorded as traumatic or minimal trauma and fracture site was documented. Biochemical data assessed included renal function, 25-hydroxy vitamin D level, parathyroid hormone (PTH) level, thyroid stimulating hormone (TSH) level, procollagen type I N-terminal propeptide (PINP), and C-terminal telopeptide of type I collagen (CTx).

Patients with a persistently low ALP level were recalled to clinic for review and repeat blood tests for ALP and a

PLP or vitamin B6 level. Genetic testing was subsequently performed to confirm a pathogenic mutation of the *ALPL* gene in relevant individuals.

The prevalence of low ALP levels across the entire hospital was compared with the prevalence in the osteoporosis clinic in which attendees are at high risk of misdiagnosis as osteoporosis and mistreatment with antiresorptive drugs.

The prevalence of low ALP levels in patients presenting with AFF was also examined in patients enrolled in the TrAFFic study from the same centre, comprising all patients with an AFF referred to the Endocrinology service from 2015 to 2020. ALP values of these patients were reviewed and analysed using the same methodology as described above.

Approval was obtained from the Human Research Ethics Board at Alfred Health prior to study initiation. This project was not funded by the hospital or external grants.

Results

Osteoporosis clinic cohort

There were 1866 patients seen in the osteoporosis clinic during eight years. Twenty-seven patients were excluded as no ALP result was available. In the remaining 1839, 168 had at least one low ALP, and 118 had a low ALP on one occasion only (group 1); none have been found to have HPP. Fifty patients had at least two low ALP results but the majority of values were within the reference range (group 2) and 7 patients had persistently low ALP levels (group 3) (Fig. 1). Using a low ALP for screening identified two patients already diagnosed with HPP prior to this study. Since the commencement of this study, genetic testing has confirmed HPP in three more patients.

The demographic data of all patients with a low ALP is shown in Table 1, with the median age being 63 years and 51% being male. Of note, 95.2% had received antiresorptive therapy. Isolated low ALP levels were most often encountered in patients having lung and/or cardiac transplantation; followed by plasma exchange or intravenous immunoglobulin, surgery, sepsis, induction chemotherapy, haemorrhage and bone marrow transplantation (Fig. 2).

The group with persistently low ALP levels is described further in Table 2. All patients had elevated vitamin B6 levels. Bone densitometry *T* scores were normal in two patients, within the osteopaenic range in two (− 1.0 to − 2.5) and within the osteoporotic range in three (< − 2.5).

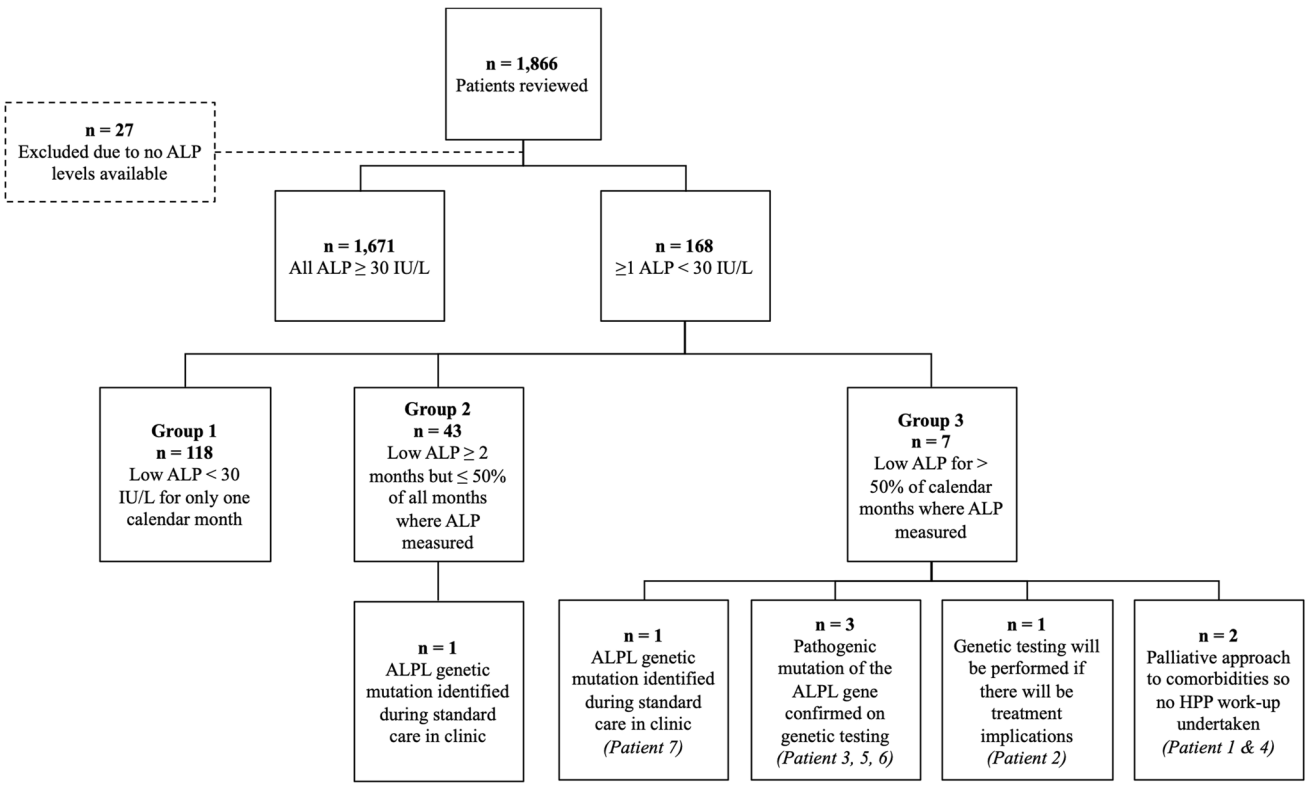

Fig. 1 Evaluation of ALP levels in patients seen in an osteoporosis clinic from 2012 to 2020

Table 1 Osteoporosis clinic patient characteristics (2012–2020)

Characteristic	All patients with a low ALP ($n=168$)	Group 1: low ALP for one month only ($n=118$)	Group 2: low ALP for ≥ 2 months ($n=43$)	Group 3: persistently low ALP ($n=7$)
Age (years)	63 (23–90)	63 (23–90)	63 (26–81)	62 (39–85)
Male, *n* (%)	86 (51.2)	56 (47.5)	26 (60.5)	4 (57.1)
ALP nadir level (IU/L)	24 (6–29)	18 (7–22)	23 (9–29)	26 (6–29)
History of fragility fracture, *n* (%)	60 (35.7)	41 (34.7)	16 (37.2)	3 (42.9)
History of avascular necrosis, *n* (%)	8 (4.8)	3 (2.5)	5 (10)	0 (0)
Atypical femoral fracture, *n* (%)	4 (2.4)	1 (0.8)	1 (2.3)	2 (28.6)
Known family history of osteoporosis, *n* (%)	19 (11.3)	14 (11.9)	5 (10)	0 (0)
History of dental issues, *n* (%)	28 (16.6)	22 (18.6)	5 (11.6)	1 (14.3)
Osteoporosis treatment received, *n* (%)	160 (95.2)	113 (95.8)	41 (95.3)	6 (85.7)
Bisphosphonate therapy, *n* (%)	153 (91.1)	111 (94.1)	37 (86.0)	5 (71.4)
Intravenous	148 (88.1)	107 (90.7)	36 (83.7)	5 (71.4)
Oral	25 (14.9)	17 (14.4)	6 (14.0)	2 (28.6)
Denosumab, *n* (%)	27 (16.1)	16 (13.6)	8 (18.6)	3 (42.9)
Teriparatide, *n* (%)	8 (4.8)	4 (3.4)	2 (4.7)	2 (28.6)
Raloxifene, *n* (%)	2 (1.2)	1 (0.8)	0 (0)	1 (14.3)
Biochemistry				
Bone turnover markers measured, *n* (%)	41 (24.4)	33 (30.0)	7 (16.3)	2 (28.6)
P1NP level (mcg/L)	27 (5.8–332) $n=31$	33 (5.8–332) $n=23$	17 (13–40) $n=6$	39 (32–46) $n=2$
CTx level (ng/L)	195 (14–1349) $n=40$	210 (14–1349) $n=33$	184 (124–345) $n=5$	183.5 (127–240) $n=2$
Vitamin D (nmol/L)	74 (14–168) $n=167$	74 (14–168) $n=117$	71 (24–144) $n=43$	78.3 (48–103) $n=7$
PTH (pmol/L)	5.4 (1.0–129.0) $n=57$	5.2 (1.0–31.0) $n=36$	5.7 (1.6–129.0) $n=18$	4.8 (2.9–7.1) $n=3$
Creatinine (μmol/L)	76 (36–270)	75 (42–227)	77 (36–270)	96 (55–168)
eGFR (mL/min/1.73m^2)	86 (19–90)	87 (19–90)	85 (20–90)	68 (38–90)
Corrected calcium (mmol/L)	2.42 (1.95–2.69)	2.42 (2.11–2.69)	2.41 (1.95–2.55)	2.47 (2.29–2.55)
Serum phosphate (mmol/L)	1.10 (0.43–1.89)	1.10 (0.52–1.59)	1.11 (0.43–1.89)	1.18 (0.78–1.55)

Data presented as median (range) unless otherwise stated

Group 1: low ALP level during one calendar month out of the patient's duration of interaction with the health service from January 2008 to April 2020

Group 2: low ALP levels in ≥ 2 months, which constituted less than half of the months where the ALP level was assessed

Group 3: low ALP levels in > 50% of all calendar months when an ALP level was measured

As shown in Table 3, fragility fractures were present in 41 of 118 (35%) patients with an isolated low ALP, 16 of 43 (37%) patients with multiple low ALP levels, and 3 of 7 (43%) with persistently low ALP levels (Table 3). In the latter group, fractures of the feet, hands, femur, wrist, and ribs were observed, not vertebral or hip fractures. Vertebral and hip fractures were present in groups 1 and 2. Two patients with persistently low ALP levels sustained an AFF, both of whom had received antiresorptive therapy prior the fracture, one with a bisphosphonate and the other with denosumab.

Hospital-wide ALP testing

In 2021, the hospital performed 175,047 ALP tests in 49,336 individuals, with 696 measurements < 30 U/L (0.4%) in 284 patients (0.6%).

TrAFFic study

Two of 22 individuals with an AFF had at least one ALP level below 30 IU/L. Both had received prolonged bisphosphonate therapy and were referred to the osteoporosis clinic

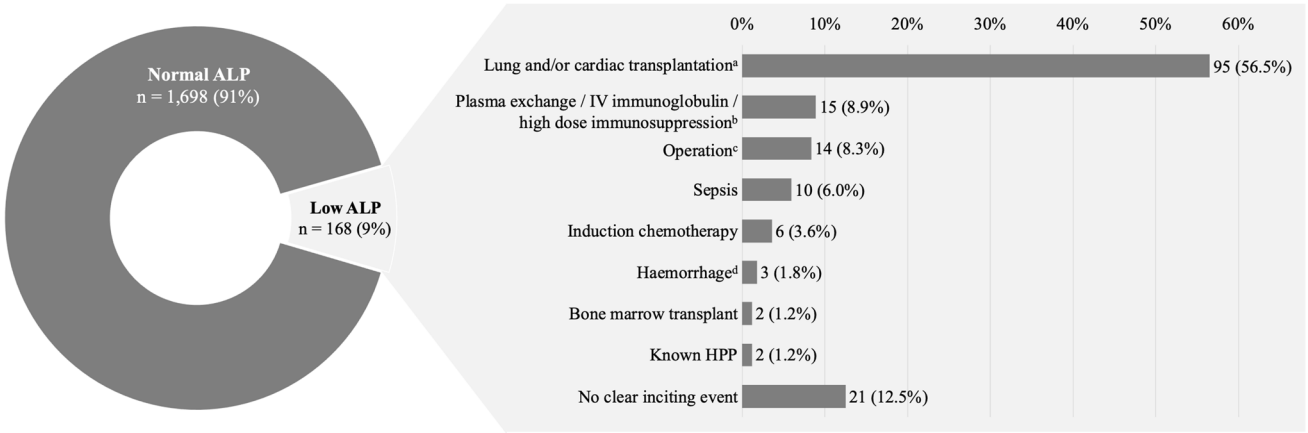

Fig. 2 Low ALP levels and surrounding circumstances. **a** Low ALP levels at time of lung transplantation in 92 (54.8%) patients, heart transplantation in 2 (1.2%) patients, and combined heart–lung transplantation in 1 (0.6%). **b** Individuals with a low ALP on the day of treatment with plasma exchange, intravenous immunoglobulin, and/or or pulse intravenous methylprednisolone. **c** Operations included coronary artery bypass graft, left ventricular assist device insertion, total hip replacement for fractured neck of femur, laparoscopic anterior resection and endoscopic procedures. **d** Haemorrhage was defined as significant bleeding requiring blood transfusion

for assessment after cessation of bisphosphonate therapy. One was been found to have a pathogenic *ALPL* mutation.

Discussion

This study reports that 9% of osteoporosis clinic attendees (168 of 1839) had ALP < 30 U/L and 4.2% (7 patients) of these had persistently low ALP levels. Five patients have been diagnosed with HPP, four in the group with persistently low ALP levels. The prevalence of HPP was 0.3% of patients in the osteoporosis clinic and 3% of patients with at least one low ALP.

The 9% prevalence of at least one low ALP in this study of osteoporosis clinic attendees is higher than that reported previously. A study in an ambulatory care endocrinology practice identified 315 of 20,000 patients (~ 1.6%) seen during one year had an ALP ≤ 40 U/L [14]. Ten patients had histories suggestive of HPP but genetic testing was not reported. An osteoporosis clinic in Edinburgh reported 16 of 3285 (0.49%) patients had an ALP level ≤ 40 U/L on at least two occasions [15]. Eight of the 16 individuals had *ALPL* mutations associated with HPP and six had potentially pathogenic *ALPL* mutations.

Hospital-wide ALP results from this study found ALP < 30 U/L in 0.4% of all tests and 0.6% of all patients who had an ALP tested in 2021, higher than reported in 0.19% of tests at a veteran centre (cut-off < 30 U/L) and 0.36% of tests in a tertiary centre in Brazil (cut-off < 40 U/L) [16, 17].

The significance of a low ALP level may not be appreciated in the clinic or hospital setting; thus, delay in diagnosis is common [12, 21, 22]. In this and other studies, patients with persistently low ALP levels form a small subset of all patients with a low ALP [23, 24].

ALPL mutations have been reported in over half of adults with low ALP levels [25–27]. A Danish study of an Endocrinology unit over 12 years described a 0.20% prevalence of persistently low ALP levels (51/26,121), and HPP was confirmed in 13 of the 24 who underwent genetic testing [25]. In another study, *ALPL* mutations were identified in 21 of 42 adults with low ALP levels [26]. Four of seven patients with persistently low ALP levels in this study have been confirmed to have HPP. One of the five patients diagnosed with HPP was classified into group 2, with multiple low ALP levels but less than half of his measured ALP < 30 U/L (the majority of his 157 ALP measurements were < 35 U/L, with a median of 34 U/L). The remaining 3 out of 7 patients with persistently low ALP levels have not undergone genetic testing; thus, there remains potential for the diagnosis of HPP to be made (Table 2).

There are many causes of a transiently low ALP level including use of antiresorptive agents, nutritional deficiencies, and acute severe illness [18–20]. Such causes are likely to be more common than HPP and so should be considered early in the evaluation of a low ALP. A large proportion of patients with transiently low ALP levels in this study were undergoing cardiac and/or lung transplantation. Cardiac bypass during these procedures is a recognised cause of low ALP. Low ALP in transplant recipients may also be multifactorial, as they receive high-dose glucocorticoid therapy.

Evidence for HPP is supported by finding a high urinary phosphoethanolamine level and serum PLP (main circulating form of vitamin B6), as these substrates of TNSALP

Table 2 Clinical features of patients with persistently low ALP levels

Pt	Age/sex	Clinical history	Reason for referral to clinic	Family history of OP	Dentition (no premature loss of deciduous teeth)	Fracture history (no malunion unless mentioned)	AFF	Proportion of low ALP[@]	Nadir ALP (IU/L, RR < 30)	Serum B6 level (nmol/L, RR 35–110)	CTx (ng/L, RR 100–1000)	P1NP (mcg/L, RR 15–115)	Baseline DXA lumbar spine (T score (BMD^))	Baseline DXA total hip (T score (BMD^))	Previous osteoporosis treatment	Clinical suspicion of HPP	Clinical outcome
1	75/female	Lung transplant for COPD Chronic rejection Chronic renal impairment stage 4	Osteopaenia prior to lung transplantation	-	Periodontitis	Atraumatic: ribs, vertebral crush fracture[#]	No	91.5% (43/47)	17	> 2000* Low zinc level, 10.2 mcmol/L	240	46	− 2.3 (0.918)	− 2.3 (0.728)	Zoledronic acid (1 dose)	No	Stable BMD and no further fractures after 4 years of follow-up. Renal impairment and palliative state resulting in decision against antiresorptive therapy so workup for HPP ceased
2	68/male	Single lung transplant for idiopathic pulmonary fibrosis	Bone health review prior to lung transplantation	-	Dental caries	No fractures	No	58.8% (10/17)	18	170	-	-	0.4 (1.133)	− 0.3 (0.986)	Zoledronic acid (3 doses)	Yes	Stable normal BMD and no fractures after 4 years of follow-up. *ALPL* gene mutation testing will be pursued if further antiresorptive therapy is needed

Table 2 (continued)

Pt	Age/sex	Clinical history	Reason for referral to clinic	Family history of OP	Dentition (no premature loss of deciduous teeth)	Fracture history (no malunion unless mentioned)	AFF	Proportion of low ALP[@]	Nadir ALP (IU/L, RR < 30)	Serum B6 level (nmol/L, RR 35–110)	CTx (ng/L, RR 100–1000)	P1NP (mcg/L, RR 15–115)	Baseline DXA lumbar spine (T score (BMD^))	Baseline DXA total hip (T score (BMD^))	Previous osteoporosis treatment	Clinical suspicion of HPP	Clinical outcome
3	39/male	Crohn's disease	Osteopaenia	-	No dental disease reported	Traumatic: clavicle, cheek, finger, ribs	No	70% (21/30)	22	487	-	-	− 1.5 (0.843)	− 2.6 (0.686)	-	Yes	Pathogenic *ALPL* mutation identified
4	62/male	Bronchiolitis obliterans Rheumatoid arthritis Sjogren's disease	Steroid induced osteoporosis	Yes	No dental disease reported	Traumatic: rib, forearm	No	51.5% (17/33)	22	-	-	-	− 2.8 (0.883)	− 3.0 (0.695)	Zoledronic acid (2 doses) Denosumab	No	No further fractures with denosumab treatment. For palliative management of pulmonary disease so workup for HPP ceased
5	85/female	Severe osteoporosis Premature menopause (age 38) Advancing dementia	Severe osteoporosis with AFF	-	Top dentures	Atraumatic: bilateral AFF[#], right femoral shaft stress fracture requiring revision of right femoral intramedullary nail[#], wrist[#]	Yes	100% (18/18)	16	284	340	34	−3.5 (0.750)	N/A	Oral bisphosphonate Raloxifene Denosumab Teriparatide	Yes	Pathogenic *ALPL* mutation identified

Table 2 (continued)

Pt	Age/sex	Clinical history	Reason for referral to clinic	Family history of OP	Dentition (no premature loss of deciduous teeth)	Fracture history (no malunion unless mentioned)	AFF	Proportion of low ALP[@]	Nadir ALP (IU/L, RR < 30)	Serum B6 level (nmol/L, RR 35–110)	CTx (ng/L, RR 100–1000)	P1NP (mcg/L, RR 15–115)	Baseline DXA lumbar spine (T score (BMD^))	Baseline DXA total hip (T score (BMD^))	Previous osteoporosis treatment	Clinical suspicion of HPP	Clinical outcome
6	61/male	Lung transplant	Osteopaenia following lung transplantation	-	Chronic periodontal disease	No fractures Sternal malunion 9 months post-transplant[#]	No	78.3% (18/23)	19	175	78	24	−0.6 (1.149)	−0.4 (1.035)	Zoledronic acid (2 doses)	Yes	Pathogenic *ALPL* mutation identified
7	41/female	Complex regional pain syndrome Epilepsy Arthritis	Bilateral AFF following 4 years of denosumab treatment	-	No dental disease reported	Atraumatic: navicular and metatarsal fractures with delayed healing; bilateral AFF[#]	Yes	100% (4/4)	7	> 2000	127	32	0.8 (1.150)	−1.7 (0.730)	Oral bisphosphonate Denosumab Teriparatide	Yes	Pathogenic *ALPL* mutation identified. Commenced teriparatide, with improved AFF healing. No further fractures

Abbreviations: *AFF* atypical femoral fracture, *BMD* bone mineral density, *COPD* chronic obstructive pulmonary disease, *CTx* C-terminal telopeptide of type I collagen, *HPP* hypophosphatasia, *OP* osteoporosis, *P1NP* procollagen type I N-terminal propeptide, *Pt* patient, *RR* reference range

[@]Occasion of low ALP/total months ALP measured

[#]Following antiresorptive therapy

[*]In context B6 supplement

^BMD in g/cm^2

Table 3 Fracture data for patient groups

	Group 1: low ALP for one month only ($n=118$)	Group 2: low ALP for ≥ 2 months ($n=43$)	Group 3: persistently low ALP ($n=7$)
History of fracture	54 (45.8)	23 (55.5)	5 (71.4)
History of atraumatic fracture	41 (34.7)	16 (37.2)	3 (42.9)
Sites of atraumatic fracture			
Foot and hand	13 (11.0)	4 (9.3)	2 (28.6)
Vertebral	24 (20.3)	7 (16.3)	0
Hip/pelvis	1 (0.8)	1 (2.3)	0
Femur	2 (1.7)	3 (7.0)	2 (28.6)
Wrist	5 (4.2)	1 (2.3)	1 (14.3)
Ribs	7 (5.9)	2 (4.7)	1 (14.3)
Hand	2 (1.7)	0	0
Humerus	1 (0.8)	0	0
Atypical femoral fracture	1 (0.8)	1 (2.3)	2 (28.6)

Data presented as *n* (%)

Group 1: low ALP level during one calendar month out of the patient's duration of interaction with the health service from January 2008 to April 2020

Group 2: low ALP levels in ≥ 2 months, which constituted less than half of the months where the ALP level was assessed

Group 3: low ALP levels in > 50% of all calendar months when an ALP level was measured

accumulate in HPP [7, 25, 26]. These biomarkers differentiate HPP from other causes of a low ALP, with serum PLP being a more sensitive and specific biomarker than urinary PEA [8]. Patients with a persistently low ALP in this study were found to have an elevated vitamin B6 after withdrawal of vitamin supplementation. These supporting biomarkers may be especially useful where antiresorptive therapy has preceded the finding of a low ALP.

Distinguishing HPP from age-related bone fragility is important due to the potential for inappropriate use of antiresorptive therapy. Bisphosphonates exacerbate the impaired mineralisation seen in HPP by compromising residual TNSALP activity [8]. Of the seven patients with persistently low ALP levels, six had received antiresorptive therapy and two sustained fragility fractures after their administration. A bone biopsy may have identified failed primary mineralisation (osteomalacia) which occurs in adults with HPP in the presence or absence of antiresorptive therapy [28–31]. The group with persistently low ALP levels had a high number of atypical fractures (Table 3). There is an increased risk of subtrochanteric and diaphyseal atypical femoral fractures in adult HPP patients, as well as metatarsal fractures [32, 33]. The evaluation of low ALP levels in the TrAFFic study cohort with AFF looks only at one subset of fracture that is more common in HPP.

This study has several limitations. As this was a retrospective survey of ALP levels in clinic and hospital patients, it was not possible to perform a systematic interrogation of all possible causes of a low ALP or to detect temporal associations between antiresorptive use and low ALP levels [19, 27]. In addition, generalisability is limited by the large transplant population and high proportion of males. Moreover, while fractures were documented, any causal relationship to underlying bone fragility, HPP, or drug therapy could not be determined. In those with low ALP, the prevalence of HPP is likely to be underestimated as genetic testing has not been undertaken in all patients. Additionally, the cut-off of ALP < 30 U/L was utilised as it is the lower limit of normal at our institution and across Australia. A higher cut-off such as that used internationally and in previous studies might have identified more patients with HPP. The case for this is supported by one of the five patients with HPP who would have been considered to have persistently low ALP (group 3 rather than group 2) if the ALP cut-off was < 35 U/L. Thus, a "low" ALP, defined as a level below the lower limit of the reference range, may benefit from further clarification.

Although HPP is a rare illness, assessment of ALP is appropriate given the illness may be misdiagnosed as osteoporosis. The potential harm lies in the prescription of antiresorptive therapy. The assessment of ALP is therefore especially relevant to patients presenting with fragility or atypical femur fractures. Persistently low ALP in osteoporosis clinic attendees should signal consideration of the diagnosis of HPP. The occurrence of a serially low ALP level is uncommon, but when found, investigating for HPP has a relatively high yield, justifying serial measurement whenever a single low level is detected.

Declarations

Conflicts of interest PRE has received research funding from Alexion. All other authors declare no conflict of interest.

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