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Adult Hypophosphatasia in Physically Active Individuals: Substrate Biochemistry (PLP, PPi, PEA), Stress-Fracture Phenotype, and Diagnostic Challenges

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Abstract

Background. Hypophosphatasia (HPP) is a rare inborn error of metabolism caused by loss-of-function ALPL variants that reduce tissue-nonspecific alkaline phosphatase activity, producing persistently low serum alkaline phosphatase (ALP) and accumulation of pyridoxal-5'-phosphate (PLP/vitamin B6). In adults, HPP may present with recurrent metatarsal and femoral stress fractures, chronic pain and reduced function, features that overlap with overtraining, Relative Energy Deficiency in Sport (REDs) and the Female Athlete Triad.

Aim. To synthesise the published literature on adult HPP in athletes and physically active individuals, focusing on recurrent stress fractures, diagnostic delay, low ALP as a red flag and PLP/vitamin B6 as substrate markers.

Brief description of the state of knowledge. Direct evidence is limited to a few case reports (runners, an archer, a woman with no specified sport) and one case-finding study; in each, low ALP was the entry-point and PLP usually elevated. A podiatry study found ALPL variants in 2 of 13 patients with metatarsal stress fracture and low ALP. Contextual cohorts confirm a high burden of fractures, pain and impaired performance independent of bone mineral density, and antiresorptive therapy is linked to atypical femoral fractures in unrecognised HPP.

Summary. Adult HPP should be considered in active individuals with recurrent or non-healing stress fractures and persistently low age- and sex-adjusted ALP. Adding ALP to the athlete bone-health work-up, with reflex PLP and ALPL testing when ALP is low, may shorten diagnostic delay and prevent inappropriate antiresorptive treatment. HPP and the Female Athlete Triad/REDs can coexist, and general adult-HPP or consensus literature should not be over-interpreted as direct evidence in athletes.

Key words: hypophosphatasia (HPP); alkaline phosphatase; stress fractures; athletes; pyridoxal phosphate; vitamin B6.

1. Introduction

Stress fractures are among the most frequent bone injuries in endurance, weight-bearing and high-volume training athletes, with the tibia, tarsal navicular, metatarsals and fibula among the most commonly affected sites. In adults with underlying metabolic bone disease, femoral stress fractures and subtrochanteric pseudofractures also occur. The general clinical and radiographic spectrum of stress and insufficiency fractures, including site distribution, imaging features, healing trajectory and links to underlying metabolic bone disease, has been comprehensively reviewed [1]. In an active adult with a stress fracture, the standard differential diagnosis

typically includes training overload, inadequate recovery, REDs and the Female Athlete Triad, eating disorders, vitamin D deficiency, low bone mineral density (osteopenia or osteoporosis) and osteomalacia [1,2,3,4].

Hypophosphatasia is far less often considered in this setting, although milder, adult-onset forms of the disease are now believed to be substantially more prevalent than previously assumed [5,6,7]. HPP results from loss-of-function variants in ALPL (alkaline phosphatase, biomineralization associated), the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). Reduced enzymatic activity allows extracellular accumulation of TNSALP substrates: inorganic pyrophosphate (PPi), a potent inhibitor of hydroxyapatite crystal growth; pyridoxal-5'-phosphate (PLP), the principal circulating form of vitamin B6; and phosphoethanolamine (PEA), whose role as a natural in vivo substrate is less firmly established [8,9,10].

In adults, HPP typically presents with metatarsal stress fractures, subtrochanteric or diaphyseal femoral pseudofractures, calcific arthropathies, dental abnormalities and musculoskeletal pain, accompanied by persistently low age- and sex-adjusted serum ALP [6,19] and elevated PLP [10,11,12,13,14,15]. The clinical picture overlaps with that of an active or competitive athlete: many patients sustain their first stress fracture during sport or running, are managed by sports-medicine teams or physiotherapists, and may be told that their injuries reflect training error, low bone density or the Female Athlete Triad [16,17,18].

Two features distinguish HPP from these more common explanations and are typically overlooked. The first is a persistently low serum ALP, a widely available and frequently underrecognised red flag in routine biochemistry, because most laboratory algorithms flag only elevated values [6,7,14,19]. The second is the substrate signature of HPP, elevated PLP/vitamin B6 (with PEA and PPi where available), which can confirm the biochemical phenotype and, together with ALPL testing, secure the diagnosis [9,20,21,22].

Despite growing recognition of HPP among bone-metabolism specialists, the literature situated at the intersection of HPP and sport or physical activity remains scarce. Most published cases of HPP in athletes or physically active individuals are isolated case reports [16,17,18,23,24,25], with an additional report of recurrent atraumatic stress fractures in active-aged adults without a specified sport [26]. The wider adult-HPP literature is rich in information about fractures, pain, function, biomarkers and treatment but rarely uses sport-related terminology; conversely, the major consensus frameworks for stress-fracture risk in athletes, the Female Athlete Triad and REDs, do not address HPP [2,3,4], even though general stress-fracture reviews note that

recurrent or poorly healing fractures should prompt a metabolic-bone work-up that includes HPP [1]. This narrative review brings these two literatures together. We first describe the very limited primary evidence on HPP in adult athletes and physically active individuals, summarise the more extensive contextual evidence on adult HPP relevant to the active patient, examine PLP/vitamin B6 and mineral metabolism in light of the substrate pathophysiology of HPP, and discuss diagnostic strategy, treatment options and the risk of misdiagnosis. Throughout, consensus references (international diagnostic criteria, REDs/Triad consensus statements, foundational PLP/B6 biochemistry) are kept clearly separate from direct evidence on HPP in athletes, so as not to overstate the strength of the evidence base.

2. Material and methods

2.1. Study design and reporting

This is a structured narrative literature review with a scoping orientation, focused on adult HPP at the intersection with sport and physical activity. A scoping/narrative format was chosen because direct primary evidence on HPP in athletes is limited and heterogeneous (case reports, small case series and one case-finding study), and a formal systematic review with meta-analysis is not feasible. The search strategy, source documentation, eligibility criteria and an explicit evidence-classification scheme were prespecified, but the review was not registered (e.g., in PROSPERO) and formal scoping-review flow accounting with independently duplicated screening and separately recorded exclusion reasons was not performed, given the heterogeneity of the included publications and the deliberate inclusion of cornerstone/background references identified outside the primary query.

2.2. Information sources and search strategy

Main bibliographic searches were performed in PubMed, Web of Science Core Collection, Embase and Scopus, targeting the intersection of HPP terminology with sport / physical-activity / exercise / stress-fracture terminology (Boolean combinations of hypophosphatasia, ALPL, alkaline phosphatase, stress fracture, athlete, runner, physical activity, exercise, Female Athlete Triad, relative energy deficiency). Searches further combined the disease entity with PLP/vitamin B6 terms (PLP, pyridoxal-5'-phosphate, vitamin B6, pyridoxine, pyridoxic acid) and mineral-metabolism terms (phosphate, calcium, vitamin D, zinc, diet). Because many key HPP, low-ALP, PLP/B6 and Female Athlete Triad/REDs publications do not use both vocabularies, supplementary records were identified through Google Scholar Labs forward and backward citation searches, hand-searching of reference lists of included reviews and case

series, and purposive inclusion of cornerstone references on HPP diagnostic criteria, ALP/PLP/PPi pathophysiology and the REDs/Female Athlete Triad frameworks. Searches were conducted up to 18 May 2026.

2.3. Eligibility criteria and evidence classification

Strict eligibility cut-offs typical of a systematic review (study design, sample-size minimum, peer-review status) were not imposed. Instead, each retrieved record was classified into one of the following categories, which structure the synthesis and are used consistently to distinguish direct from indirect evidence:

Category A, Primary evidence on HPP in athletes / physically active individuals: case reports, case series and case-finding studies in which a sport, athletic discipline or substantial physical activity is explicitly described in the context of HPP-related stress fractures or pseudofractures.

Category B, Contextual adult-HPP evidence: clinical, epidemiological and registry studies, reviews and case series describing adult HPP without an explicit athlete framing but providing the clinical context (fractures, pseudofractures, pain, function, BMD, atypical femoral fractures, registries, burden of illness).

Category C, Diagnostic, screening and genotype/phenotype evidence: studies of low-ALP populations, ALP thresholds, ALPL genotyping yield, diagnostic criteria and diagnostic delay.

Category D, PLP/vitamin B6 and mineral metabolism: foundational and current literature on TNSALP substrates, B6 vitamers, dietary mineral intake and enzyme replacement or alternative therapies.

Background / cornerstone references: International Working Group HPP diagnostic criteria, IOC REDs consensus statement, Female Athlete Triad consensus statement and foundational alkaline phosphatase biochemistry. These are used as framing and background, never as direct evidence of HPP behaviour in athletes.

In this review, the term primary evidence is reserved for Category A studies directly describing HPP in athletes or physically active individuals. The broader term search-derived studies retained for narrative synthesis refers to all retained records from the database and Google Scholar Labs searches that contributed to the narrative synthesis, including contextual Category B/C/D evidence.

Records were excluded if they were animal-only or in vitro-only studies without direct clinical relevance to HPP, purely technical or biomaterial papers, ALP/ALPL publications unrelated to

clinical HPP, dental-only odonto-HPP reports without skeletal or diagnostic relevance, or publications on unrelated metabolic bone diseases without relevance to stress fractures, low ALP, PLP/vitamin B6 or mineral metabolism. Conference abstracts, editorials and letters without primary clinical data were excluded unless they provided otherwise unavailable case-level detail directly relevant to HPP in athletes or to one of the diagnostic-framework themes of the review.

Where individual figures (ALP, PLP, age, fracture counts, BMD/T-scores, percentages, P values) are cited below, they reflect values explicitly reported in the source paper and verified against the full text; where verification was not possible, the cited paper is referenced at the level of its title or general claim only.

2.4. Synthesis approach

Evidence was synthesised narratively rather than meta-analytically. Within each section we first present the Category A primary evidence on athletes, then the Category B contextual evidence relevant to active patients, and finally the Category C/D and background material on diagnosis, biomarkers, treatment and overlap with REDs and the Female Athlete Triad. We deliberately avoid pooling effect estimates or presenting consensus references or non-athlete adult-HPP cohorts as if they directly described HPP in athletes, and we flag explicitly any extrapolation from adolescent cases (16-20 years) to adult-onset HPP in older athletes.

2.5. Literature search and selection summary

A literature search and selection summary is presented in Table 1 to provide transparency on the search yield and study selection process for this structured narrative review. Because the review combined four structured database searches (PubMed, Web of Science Core Collection, Embase, Scopus) with Google Scholar Labs citation-discovery, hand-searching of reference lists and purposive inclusion of cornerstone/background references identified outside the primary query, exact counts for duplicate removal, title/abstract exclusions and full-text exclusions were not recorded separately at the level of a formal scoping-review flow diagram. Only aggregated identification and inclusion counts are therefore reported. The final search-derived pool comprised 432 records from databases and Google Scholar Labs. Of these, 53 search-derived studies were retained for direct and contextual narrative synthesis (Category A primary evidence and Category B/C contextual adult-HPP evidence, including selected Category D records on PLP/B6 and mineral metabolism that emerged from the structured searches). The remaining 379 search-derived records were not retained after deduplication,

title/abstract screening, eligibility assessment or scope assessment; exact counts for each exclusion step were not recorded separately. In addition, 16 unique background/cornerstone references were included separately for diagnostic, mechanistic and sports-medicine framing, including HPP diagnostic criteria, foundational ALP/PLP/PPi pathophysiology papers, low-ALP diagnostic algorithms, and RED-S/Female Athlete Triad consensus statements. These references were not part of the 432 search-derived pool and were not treated as direct evidence on HPP in athletes unless they directly described athletes or physically active individuals. The final manuscript corpus therefore comprised 69 references: 53 search-derived studies and 16 background/cornerstone references.

Table 1. Literature search and selection summary.

Stage	Source / step	Records, n	Notes
Identification	PubMed	68	Structured database search.
	Web of Science	36	Structured database search.
	Embase	204	Structured database search.
	Scopus	76	Structured database search.
	Total records identified from databases	**384**	**Before deduplication across databases.**
Additional identification	Google Scholar Labs search 1	31	Supplementary citation-discovery / snowballing source.
	Google Scholar Labs search 2	31	Supplementary citation-discovery / snowballing source.
	Total Google Scholar Labs records before internal deduplication	**62**	**Raw Google Scholar Labs suggestions.**
	Duplicates removed between the two Google Scholar Labs searches	14	Internal deduplication of Google Scholar Labs results only.
	Unique Google Scholar Labs records	**48**	**Supplementary records after removal of duplicates between the**

			two Google Scholar Labs searches.
	Total records identified from databases and Google Scholar Labs	**432**	**384 database records + 48 unique Google Scholar Labs records.**
Supplementary background identification	Hand-searching, citation chasing and purposive cornerstone/background references	Not added to main numeric count	Used to identify key diagnostic criteria, ALP/PLP/PPi pathophysiology papers, low-ALP diagnostic algorithms and RED-S/Female Athlete Triad consensus documents.
Screening / eligibility	Search-derived records not retained after deduplication, title/abstract screening, eligibility assessment or scope assessment	379	Calculated as 432 search-derived records minus 53 search-derived studies included in the narrative synthesis. Additional cornerstone/background references were included and reported separately (see following rows). Exact split between duplicates, title/abstract exclusions and eligibility exclusions was not separately recorded.
Included	Search-derived studies retained for narrative synthesis	53	Includes Category A primary evidence and Category B/C/D contextual evidence identified from database searches and Google Scholar Labs.
	Additional background / cornerstone references included separately	16	Diagnostic criteria, RED-S/Female Athlete Triad, low-ALP algorithms, PLP/B6 and pathophysiology references.
	Total records included in the manuscript	**69**	**53 search-derived synthesis studies + 16 unique**

			additional/background references.

Note. This table reports a identification and selection summary for a structured narrative review with a scoping orientation. The 432 search-derived records comprise 384 database records before between-database deduplication and 48 unique Google Scholar Labs records after internal deduplication of two Google Scholar Labs searches. Of these, 53 search-derived studies were retained for direct and contextual narrative synthesis, leaving 379 search-derived records not retained. Sixteen background/cornerstone references were purposively included separately for diagnostic, mechanistic and sports-medicine framing and were not part of the main search-derived pool. Because the review combined structured database searches with Google Scholar Labs citation discovery, hand-searching and purposive inclusion of background references, exact counts for duplicate removal, title/abstract exclusions and full-text exclusions were not recorded separately. The final manuscript corpus comprised 69 references: 53 search-derived studies and 16 background/cornerstone references.

3. Results

3.1. Study selection and overall description of the literature

Across the included literature, only a small subset of publications describe HPP directly in athletes or in physically active adults (primary evidence; Section 3.2). These are predominantly individual case reports of female runners, an archer, a woman with recurrent atraumatic stress fractures and no specified sport, and adolescent athletes, supplemented by one electronic-health-record case-finding study in adults presenting to a podiatry clinic with metatarsal stress fracture [16,17,18,23,24,25,26,27]. Seven of the primary publications are single-patient case reports, and no controlled studies, prospective cohorts or randomised trials specifically focused on HPP in athletes were identified. This pattern broadly mirrors the wider adult-HPP literature, in which prospective trial-level evidence is limited to a small number of enzyme-replacement studies in mixed adolescent and adult populations rather than in athletes [28], and should be borne in mind when interpreting the synthesis below. The remainder of the evidence base consists of contextual adult-HPP cohorts and case series (Section 3.3), diagnostic studies of low ALP and ALPL testing (Section 3.4), publications on PLP/vitamin B6 and mineral metabolism (Section 3.5), and treatment- or functional-outcome studies (Section 3.6), with background and cornerstone references on HPP nosology, alkaline phosphatase biology and the REDs/Female Athlete Triad frameworks supporting the clinical reasoning.

3.2. HPP in athletes and physically active individuals

3.2.1. Recurrent stress fractures in adult female runners

Two case reports describe adult female runners in whom recurrent stress fractures led to a diagnosis of HPP. Fanous and Barb reported a 49-year-old woman, previously healthy and an avid runner for several years before her first injury, who sustained seven fractures over the preceding two years, including multiple metatarsal stress fractures, a left proximal femoral shaft stress fracture and a rib fracture, with delayed healing (8-12 weeks). The initial work-up (DXA, vitamin D, calcium, parathyroid hormone, FGF23, urine and serum protein electrophoresis) was unremarkable except for a mildly reduced ALP of 31 U/L (reference 33-115). Bone-specific ALP was 3.3 µg/L (reference 5-18.2) and serum PLP/vitamin B6 was 52 ng/mL (reference 2.1-21.7), more than twice the upper limit of normal. Genetic testing identified a heterozygous ALPL variant c.407G>A (p.Arg136His), previously reported in infantile, odonto- and adult HPP. Asfotase alfa was initiated but discontinued after an allergic reaction, after which the patient sustained additional stress reactions and reduced her running [16].

Ryan and colleagues reported a 38-year-old female runner with recurrent right-leg pain, a grade-3 stress reaction with marrow oedema on MRI, and a history of multiple stress reactions in the tibia and feet. The patient denied vitamin supplementation, had regular menstrual cycles, successful pregnancies, a healthy body image and good nutrition, making REDs unlikely. The initial laboratory work-up was unremarkable except for low ALP at 28 U/L (reference 44-147), repeatedly confirmed; she also had severe iron deficiency and gluten intolerance. Osteocalcin and bone-specific ALP were normal and DXA Z-scores at lumbar spine and hip were above -1.0, while vitamin B6 was elevated at 186.6 nmol/L (reference 20-125). A pathogenic ALPL variant was confirmed after referral to an HPP specialist and a genetic counsellor. The patient was started on enzyme replacement therapy and within a few months returned to 5 km runs and moderately strenuous hikes; at three years of follow-up there had been no further stress fractures [18].

3.2.2. A college runner whose HPP was unmasked by the Female Athlete Triad

Fink and colleagues described a 20-year-old female NCAA Division-I cross-country and track runner referred to endocrinology for evaluation of bone health in the setting of three metatarsal stress reactions and fractures. The case is methodologically important for two reasons. First, the patient had a long childhood history of activity-related lower-limb pain ("porcupine quills in her shins" after prolonged standing, dating to approximately age 9) and shin splints from age 12, together with a maternal aunt with premature tooth loss, bone pain with running and stress

fractures. Second, her clinical picture met the Female Athlete Triad: irregular menses managed with oral contraceptives, low bone mass for age (lumbar-spine Z-score -1.6; left femoral neck 0.2; right femoral neck 1.0) and new dietary restrictions (vegetarian diet) after starting college, with weekly mileage up to ~60 miles and a BMI of 19.5 kg/m². The triad initially seemed to explain her injuries [17].

On laboratory testing her ALP was undetectable (<25 U/L; reference 39-117 for females older than 18), with calcium 9.5 mg/dL and phosphorus 3.9 mg/dL. After discontinuing the oral contraceptive pill and a B6-containing multivitamin (for one week, to avoid falsely elevating vitamin B6), ALP remained undetectable and vitamin B6 was elevated at 195.9 nmol/L (reference 20-125). ALPL testing showed an exon-4 heterozygous mutation, and pediatric-onset HPP was diagnosed because the patient's symptoms had begun before age 18. With targeted sports nutrition (energy intake increased from ~29.15 to 42.4 kcal/kg/day), discontinuation of the OCP and initiation of asfotase alfa, monthly menses resumed without synthetic hormones, ALP improved to 35 U/L once a positive energy balance was achieved, and the athlete completed her running season without recurrent fractures [17]. Two implications follow: the Female Athlete Triad and HPP are not mutually exclusive, and ALP, which is not part of the standard triad work-up, may be the only abnormality detectable on routine biochemistry. We flag this case explicitly as adolescent/young-adult with childhood onset, and are cautious in extrapolating its findings to typical mid-life adult-onset HPP.

3.2.3. Atraumatic metatarsal stress fractures and young-adult osteoporosis

Christidis and colleagues described a 35-year-old woman referred for evaluation of recurrent atraumatic stress fractures of the metatarsals with prolonged healing. DXA showed osteoporosis at a young age, with a T-score of -2.6 at the total left hip. ALP was reduced at 14 U/L (reference 35-104); other markers of bone metabolism were unremarkable, and secondary causes of low ALP were excluded. ALPL sequencing identified heterozygous c.416G>A and c.571G>A variants, the latter one of the most common variants in adult HPP and the former typical of childhood HPP; each parent was confirmed as a carrier. Vitamin B6 was within the normal range – the authors noted that PLP elevation is typical of severe forms of HPP, illustrating that PLP is not always markedly elevated in mild adult HPP. Bisphosphonates were avoided and the patient was treated with teriparatide for two years [26]. The combination of recurrent atraumatic stress fractures, young-adult osteoporosis and reduced ALP is a reproducible HPP signature that a routine osteoporosis work-up will detect if low ALP is not overlooked. We note that the published report does not specify a competitive sport; the case is

therefore treated here as an example of recurrent atraumatic metatarsal stress fractures in a young, active-aged woman rather than as direct evidence about competitive athletes.

3.2.4. Unusual stress fracture in a professional archer

Yavuz and colleagues reported a 45-year-old professional archer with a left ulnar stress fracture at the proximal metaphysis, who had previously been treated unsuccessfully for tenosynovitis, epicondylitis and myalgia. His history was notable for HPP diagnosed ten years earlier and bilateral femoral neck stress fractures treated with percutaneous screwing. MRI excluded other pathology, and he was managed conservatively with arm slings, restriction of sporting activity for six weeks and a graduated return once callus formation was observed [25]. This case is instructive for two reasons. First, the fracture site (proximal ulnar metaphysis) is not the canonical metatarsal/femoral location of adult HPP; the authors attribute it to the high torsional force transmitted through the forearm during archery. Second, it illustrates that an established HPP diagnosis does not protect against repeated, atypically located fractures, and that fracture-related extremity pain in a known HPP patient should not be ascribed to soft-tissue diagnoses without imaging.

3.2.5. Adolescent athletic cases (with explicit caveat against direct adult extrapolation)

Two further reports describe adolescent athletes and are included with the explicit caveat that adolescent HPP cases should not be used to characterise mid-life adult-onset HPP. Kato and colleagues reported an 18-year-old Japanese female with benign prenatal HPP whose left tibial pseudofracture had developed at age 17 after months of repetitive gymnastic exercise and persisted for over a year before referral. Initial ALP at birth had been 11 U/L (reference 38-113), and ALPL testing showed compound heterozygous variants. Asfotase alfa produced pain relief within two months, disappearance of nuclide accumulation on bone scintigraphy and radiographic union at two years [23].

Windels and colleagues described a 16-year-old girl with a previously diagnosed heterozygous pathogenic ALPL variant. Her index injury was a non-union of a fifth-metatarsal fracture sustained after a minor supination injury during daily activity, which remained unhealed 17 weeks after diagnosis despite immobilisation. Her broader musculoskeletal phenotype included a prior atraumatic third-metatarsal stress fracture with six-month delayed healing, bone-marrow oedema lesions and a lumbar-spine Z-score of −2.2. After 13 weeks of asfotase alfa, cone-beam CT showed complete consolidation of the fracture, bone mineral density in the fracture gap increased by 36%, and PLP decreased on laboratory follow-up [24]. The authors note that recurrent and poorly healing fractures are documented in 36.5% of adults in the Global HPP

Registry [31], supporting the relevance of HPP as an explanation for non-healing metatarsal fractures, whether stress-related or arising after minor trauma, in selected paediatric and adolescent patients. We restate that adolescent metabolic bone biology differs substantially from that of adults in their thirties or forties.

3.2.6. Case-finding in adults with metatarsal stress fracture

Koehler and colleagues conducted a single-site, retrospective electronic-health-record case-finding study. Of 1,611 adults aged 18 years or older with a coded metatarsal stress fracture diagnosis over a six-year period, 937 (58%) had a recorded ALP measurement. Thirteen patients (1.4% of those with measured ALP) had a low ALP value; of these, eight consented to genotyping, and two carried pathogenic or likely-pathogenic heterozygous, autosomal-dominant ALPL variants, a prevalence of 0.12% (2/1,611) in unselected metatarsal stress fracture, 0.21% (2/937) in those with any ALP measurement and 15% (2/13) in those with metatarsal stress fracture and low ALP. The variants were c.318G>C (p.Gln106His) in case 1 and c.407G>A (p.Arg136His) in case 2. Both cases had multiple metatarsal and other non-metatarsal fractures and childhood symptoms recognised only retrospectively – fatigue and poor dentition in both, with chronic lower-extremity pain attributed to 'growing pains' and full upper-arch dental extraction by early adulthood in case 1, and chronic muscle weakness and multiple crowns/root canals in case 2. Both reported markedly worse pain and disability than controls with low ALP and no variant, including higher Brief Pain Inventory worst-pain scores (8.0 vs 0.8) and a higher Health Assessment Questionnaire Disability Index (1.4 vs 0) [27]. The yield of two confirmed cases in eight genotyped patients is a case-finding signal within a doubly enriched population (metatarsal stress fracture and recorded low ALP), not a population prevalence; it supports the central pragmatic message of this review.

Across the primary evidence, several of the index cases [16,17,18] explicitly recommend including HPP in the differential diagnosis whenever recurrent stress fractures, low or low-normal ALP, or elevated vitamin B6 are encountered in a physically active patient, regardless of whether the working diagnosis is overuse, REDs, the Female Athlete Triad or low BMD-for-age. The primary evidence is summarised in Table 2.

Table 2. HPP in athletes and physically active individuals.

Source	Population (age, sex, activity)	Fracture / clinical presentation	ALP / PLP-B6 and ALPL findings	Outcome

Fanous & Barb [16]	49-y woman; avid marathon runner	7 stress fractures in 2 y (metatarsals, left proximal femoral shaft, rib); delayed healing 8-12 wk	ALP 31 U/L (33-115); bone-specific ALP 3.3 µg/L (5-18.2); B6 52 ng/mL (2.1-21.7); ALPL c.407G>A (p.Arg136His) het	Asfotase alfa initiated, discontinued after allergic reaction
Ryan et al. [18]	38-y woman; runner	Grade-3 stress reaction with marrow oedema; recurrent tibial/foot stress reactions	ALP 28 U/L (44-147); B6 186.6 nmol/L (20-125); normal DXA Z-scores; pathogenic ALPL variant	Asfotase alfa; returned to 5 km running and hikes; fracture-free at 3 y
Fink et al. [17]	20-y woman; NCAA Division-I cross-country and track runner	Multiple metatarsal stress fractures, delayed healing; lumbar Z -1.6; Female Athlete Triad criteria met	ALP undetectable (<25 U/L; ref 39-117); B6 195.9 nmol/L (20-125); ALPL exon-4 het; maternal-aunt family history	Sports nutrition, OCP stopped, asfotase alfa; ALP rose to 35 U/L; season completed without recurrence
Christidis et al. [26]	35-y woman; activity not specified in report	Recurrent atraumatic metatarsal stress fractures; osteoporosis (left hip T -2.6)	ALP 14 U/L (35-104); B6 within reference range; ALPL c.416G>A + c.571G>A het	Bisphosphonates avoided; teriparatide 2 y; both parents carriers
Yavuz et al. [25]	45-y man; professional archer	Left ulnar proximal-metaphysis stress fracture; prior bilateral femoral-neck stress fractures	Known adult HPP with low serum ALP	Conservative management (slings, 6 wk activity restriction), graduated return after callus

Kato et al. [23]	18-y Japanese female; gymnast	Left tibial pseudofracture after repetitive gymnastics; benign prenatal HPP	ALP 11 U/L at birth (38-113); compound heterozygous ALPL	Asfotase alfa: pain relief at 2 mo, radiographic union at 2 y (adolescent caveat)
Windels et al. [24]	16-y girl; adolescent	5th-metatarsal fracture, unhealed 17 wk after diagnosis; prior 3rd-MT stress fracture; lumbar Z -2.2	Persistently low ALP; elevated PLP; pathogenic ALPL variant	Asfotase alfa: full consolidation at 13 wk; BMD in fracture gap +36%; PLP decreased (adolescent caveat)
Koehler et al. [27]	1,611 adults with metatarsal stress fracture (podiatry clinic); 937 with ALP, 13 low, 8 genotyped	Case-finding: 2/8 with pathogenic/likely-pathogenic het ALPL variants; multiple metatarsal/other fractures	Variants c.318G>C (p.Gln106His) and c.407G>A (p.Arg136His); 15% (2/13) of MSF + low ALP	Proof-of-concept for ALPL-based case-finding; cases had worse pain/disability (HAQ-DI 1.4 vs 0)

Notes: ALP = alkaline phosphatase; B6 = vitamin B6; DXA = dual-energy X-ray absorptiometry; het = heterozygous; MT = metatarsal; MSF = metatarsal stress fracture; OCP = oral contraceptive pill; PEA = phosphoethanolamine; PLP = pyridoxal-5'-phosphate. Reference ranges are laboratory-specific. Kato [23] and Windels [24] are adolescent cases included with an explicit age caveat.

3.3. Contextual evidence on adult HPP relevant to the active patient

3.3.1. Fracture pattern, atypical femoral fractures and the bisphosphonate trap

Adult HPP characteristically causes recurrent metatarsal stress fractures and subtrochanteric or diaphyseal femoral pseudofractures that can radiographically resemble atypical femoral fractures (AFFs) associated with long-term antiresorptive therapy [11,13,15,32]. Genest and Seefried evaluated 150 adult HPP patients in a single-centre: 15 (10%) had a subtrochanteric or diaphyseal femoral fracture, with bilateral involvement in 10 of these 15. Fracture morphology met formal AFF criteria in 88% of these fractures, and the authors argued that such fractures are intrinsic to HPP rather than truly "atypical." Disease-inherent risk factors included autosomal-recessive childhood-onset HPP, ALP at or below 20 U/L, PLP more than three times

the upper limit of normal and, paradoxically, high lumbar-spine BMD; striking extrinsic risk factors were hypovitaminosis D in 80%, prior bisphosphonates in 46.7% and proton-pump inhibitors in 40% [33].

Lefever and colleagues described 19 adults with HPP (median age 45 years; ALPL variant in 17 of 19): 7 of 19 (37%) had been inappropriately treated or planned for treatment with antiresorptive agents, and two developed AFFs after exposure to bisphosphonates and/or denosumab [34]. Sutton and colleagues reported the first case linking bisphosphonate exposure to atypical femoral fractures in adult HPP, a 55-year-old woman treated with alendronate then zoledronate for presumed osteoporosis who sustained bilateral subtrochanteric femoral fractures after four years of exposure; her serum ALP was low at 41 U/L (reference 50-136), plasma PLP was markedly elevated at 346 nM (reference 7-107), urinary PEA was raised, and ALPL sequencing identified a heterozygous c.212G>A (p.Arg71His) variant [35]. The reverse perspective, what proportion of patients labelled with AFF have biochemical or genetic signs of HPP, was addressed by Tsiantouli and colleagues: among 72 adults with confirmed AFF, 18 (25%) had at least one serum ALP value at or below 40 IU/L, but these low values were mostly attributable to concurrent antiresorptive treatment and a pathogenic ALPL variant was identified in only one patient, leading the authors to conclude that low serum ALP has low specificity for HPP in this setting [36]. Braunstein's report of an adult with multiple fractures, pain and severe disability illustrates the cumulative picture when adult-onset HPP is missed for years [37]. Two practical points follow: persistent or unexplained low ALP should be excluded before initiating antiresorptive therapy for presumed osteoporosis in an adult with fragility fracture, and in an athlete or physically active adult with low ALP and recurrent metatarsal or femoral stress fractures, bisphosphonates and denosumab should be avoided pending HPP work-up because antiresorptive treatment can worsen the underlying mineralisation defect [13,34,38,39].

3.3.2. Bone mineral density: not a reliable surrogate

Several lines of evidence indicate that BMD alone does not capture the fracture risk of adult HPP. Hepp and colleagues, in a Danish national cross-sectional study of 40 adults with HPP and 40 matched healthy controls, showed that the higher prevalence of non-vertebral low-energy fractures in HPP ($P<0.001$) was not explained by lower BMD: lumbar-spine, total-hip, femoral-neck, forearm and whole-body BMD did not differ between groups, whereas the bone-formation marker N-terminal propeptide of type 1 procollagen (P1NP) was significantly lower

in HPP (P=0.006). Adults with HPP also had reduced walking capability, lower body strength and more chronic pain [40]. Genest and colleagues, in a separate cohort of 110 adult HPP patients (84 women; mean age 46.2 years), reported a mean lumbar-spine T-score of -0.1 and a mean total-hip T-score of -1.07; lower ALP and higher PLP/PEA correlated with higher lumbar-spine T-scores, and increased lumbar-spine BMD was associated with increased risk of HPP-related fractures (22 of 110 patients, of whom 21 had biallelic mutations) [41]. For athletes, a normal or above-average DXA at the lumbar spine does not exclude HPP-related fracture risk and may, in severe disease, paradoxically reflect more compromised mineralisation; ALP is the more useful screening marker.

3.3.3. Pain, fatigue, function and quality of life

Adults with HPP report a burden of musculoskeletal pain, muscle weakness, fatigue and neuropsychiatric symptoms that affects function and quality of life. In a single-centre evaluation of 15 adults with HPP (median age 44; 73% women; 33% on enzyme replacement therapy), the 6-minute walk distance was substantially reduced (420 m vs 620 m in the general population, P<0.00005), 10-metre walk speed was slower and upper-extremity dexterity was diminished; Fatigue Severity Scale scores were well above the healthy median (5.21 vs 2.3, P<0.00005), and depression, anxiety and stress scores were elevated [42]. These findings are consistent with the Global HPP Registry burden-of-illness analysis of 304 adults (median age 48.6 years; 74% women), in which 62% had a history of at least one fracture or pseudofracture and 38% had experienced five or more HPP manifestations [43]. A cross-sectional Global HPP Registry analysis comparing 300 adults with overt skeletal manifestations and 73 with muscular or pain manifestations but no skeletal disease found comparable disability and quality-of-life impairment in both groups (similar HAQ-DI scores and 6-minute walk distances), although the skeletal group had a younger median age at first HPP manifestation (12.3 vs 22.1 years) [44]. The Högler registry analysis showed that the earliest reported manifestation occurred at a median age of 37.6 years in adults while diagnosis was made at a median of 47.5 years, a delay of approximately ten years, with pain reported in 74.5%, orthopaedic procedures in 44.6% and recurrent or poorly healing fractures in 36.5% [31].

Smaller cohorts confirm the same picture across health systems: a Spanish cohort with musculoskeletal pain and muscular weakness as the leading symptoms and identification of a new ALPL variant [45]; a Mayo Clinic series of adults with metatarsal and femoral fractures and substantial diagnostic delay [12]; a UK general-rheumatology series of 14 adults diagnosed after a median delay of 13 years, with peripheral joint pain, early-onset calcium pyrophosphate

deposition and prior fractures [46]; a UK metabolic-bone-clinic comparison of adults with HPP and adults with low BMD, identifying ALP/PLP biomarker thresholds [47]; and a report of mild adult HPP presenting de novo in the eighth decade with bone pain and fatigue [48]. The symptom burden of adult HPP overlaps with the rheumatology and sports-medicine differential of fibromyalgia, chronic fatigue, regional pain syndromes and overtraining, so that when an athlete's training load decreases because of pain, fatigue or recurrent injury, the underlying metabolic explanation is easily missed [19,34,46].

3.3.4. Calcific arthropathies and joint manifestations

Calcium pyrophosphate deposition disease, chondrocalcinosis and calcific periarthritis are characteristic non-fracture manifestations of adult HPP [11,13,14]. McKiernan and colleagues found persistent hypophosphatasaemia (ALP ≤30 IU/L) in approximately 1 in 1,544 adults, with significantly more crystalline arthritis, orthopaedic surgery, chondrocalcinosis, calcific periarthritis, enthesopathy and diffuse idiopathic skeletal hyperostosis than the general population [14]. In the same cohort, women with persistent hypophosphatasaemia had an approximately 4.5-fold higher risk of calcium pyrophosphate deposition disease and a 2.5-fold higher risk of metatarsal or femoral stress fracture, while men more often showed hypermobility and myopathic features including generalized weakness [14]. Briot and Roux, reviewing this evidence, stress that HPP should be investigated when chondrocalcinosis is found in a young adult [13]. Pseudo-gout in a young or middle-aged athlete should therefore prompt a serum ALP check, since calcific arthropathy may be the leading or only adult HPP feature. The principal contextual cohorts are summarised in Table 3.

Table 3. Contextual adult-HPP evidence (Category B/C): representative cohort, registry and case-series studies.

Source	Design / cohort	Key skeletal and clinical findings	Diagnostic insight / relevance
Berkseth et al. [12]	Retrospective single-centre (Mayo Clinic)	Metatarsal and femoral fractures, pseudofractures; substantial diagnostic delay	Cornerstone description of the adult-HPP phenotype
Hepp et al. [40]	National cross-sectional (Denmark); 40 HPP vs 40 matched controls	More non-vertebral low-energy fractures (P<0.001); BMD not different from controls; lower P1NP;	Fracture risk is not explained by DXA-BMD, supporting

		reduced walking and strength; more chronic pain	biochemical screening
Genest & Seefried [33]	Single-centre cohort; 150 adult HPP	15/150 (10%) subtrochanteric/diaphyseal femoral fractures, bilateral in 10/15; 88% met AFF criteria; prior bisphosphonates 46.7%; hypovitaminosis D 80%	Femoral fractures are intrinsic to HPP, "not atypical at all"
Genest et al. [41]	Retrospective DXA cohort; 110 adults	Mean lumbar T -0.1, total-hip T -1.07; lower ALP / higher PLP-PEA correlate with HIGHER lumbar T; 22/110 fractured	DXA underestimates fracture risk in adult HPP
Lefever et al. [34]	Single-centre case series (Belgium); 19 adults	Fractures in 74%; 2 AFFs after bisphosphonate/denosumab; biallelic carriers had lower ALP and higher PLP/PEA	Misdiagnosis as osteoporosis common; empirical pyridoxine ineffective for non-seizure symptoms
McKiernan et al. [14]	Large EHR cohort; 885,165 patients	Persistent ALP ≤30 IU/L in ~1/1,544 adults; enriched crystalline arthritis, chondrocalcinosis, enthesopathy	Defines the clinical signature of adults flagged by low ALP
Dahir et al. [44]; Seefried et al. [43]	Global HPP Registry (cross-sectional / burden-of-illness)	Muscular pain and skeletal disease comparably impair disability and QoL; 62% ≥1 fracture/pseudofracture; 38% ≥5 manifestations	Systemic burden extends well beyond fractures
Högler et al. [31]	Global HPP Registry (initial findings)	Adult earliest manifestation median 37.6 y; diagnosis 47.5 y (~10-y delay); pain 74.5%; recurrent/poorly-healing fractures 36.5%	Quantifies diagnostic delay in adults
Tsiantouli et al. [36]	Cohort of 72 adults with confirmed AFF	Low ALP (≤40 IU/L) in 25%, mostly attributable to antiresorptive treatment; pathogenic ALPL variant in only 1 patient	Low serum ALP has low specificity for HPP among AFF patients
Sutton et al. [35]	Index case report	55-y woman; alendronate then zoledronate for 4 y;	First report of bisphosphonate

		bilateral subtrochanteric femoral fractures; ALP 41 U/L; PLP 346 nM; urine PEA raised; ALPL c.212G>A (p.Arg71His) het	exposure preceding AFF in adult HPP
Kato [23]; Al-Saoudi [49]	Case reports	Pseudofracture resolution after asfotase alfa; bilateral pseudofracture healing after teriparatide	Anabolic/enzyme response in adult pseudofractures
Braunstein [37]; Calmarza [45]; Maheshwari [48]; Sodi and Hall [50]	Cohort / case reports	Musculoskeletal pain and weakness predominate; late-life and recurrent-fracture presentations with low ALP as the entry-point	Breadth of adult phenotype and diagnostic delay

Notes: AFF = atypical femoral fracture; BMD = bone mineral density; EHR = electronic health record; QoL = quality of life. Kato [23] is an adolescent/young-adult case included for its detailed radiographic documentation of pseudofracture healing under asfotase alfa.

3.4. Diagnostic challenges: low ALP as a red flag and the role of ALPL

3.4.1. ALP threshold and biochemical work-up

The cardinal biochemical finding of HPP is a persistently low age- and sex-adjusted serum ALP. Two large laboratory-based analyses define the scale of the issue. Schmidt and colleagues analysed 6,918,126 ALP measurements from adults older than 18 in a single German laboratory; 8.46% had a value below 30 U/L, and among those with a follow-up PLP measurement 6.09% had elevated PLP, suggesting a laboratory signal compatible with HPP in approximately 0.52%, about 1 in 194, of sampled adults, and the authors recommended automatic PLP measurement and clinician notification whenever low ALP is encountered [6]. Tornero and colleagues screened a large laboratory population, identified adults with persistent hypophosphatasaemia (at least two ALP values ≤35 IU/L) after exclusion of secondary causes, and detected ALPL variants in roughly half; an ALP threshold below 25 IU/L showed a specificity of 97.8% and a positive predictive value of 94.4% for detecting an ALPL variant [7]. The German multicentre study of 849 adults with at least one low ALP value found that patients with HPP more often reported musculoskeletal pain and fractures than non-HPP patients, identified 35 additional patients with four or more HPP-typical signs but no formal diagnosis, and recorded hypothyroidism in 26.3% (215/817) of the non-HPP low-ALP group [51]. The structured approach to a patient with low serum ALP, review of secondary causes,

repeat measurement to confirm persistence, work-up of HPP substrates and judicious ALPL sequencing, is summarised in a practical algorithm [19], and dedicated diagnostic recommendations for identifying adult HPP in routine clinical settings have been proposed [52].

3.4.2. Distinguishing HPP biochemically from osteoporosis

Several studies provide thresholds that help separate adult HPP from other metabolic bone disease. In a comparison of adults with confirmed HPP (n=20) and low-BMD osteoporosis controls (n=21), a total serum ALP ≤43 IU/L combined with a plasma PLP ≥120 nmol/L correctly classified the two groups, with HPP patients showing roughly three-fold lower ALP and seven-fold higher PLP and no significant differences in P1NP, osteocalcin or parathyroid hormone [47]. Genotype-phenotype work shows that biallelic (homozygous or compound-heterozygous) carriers have lower ALP, higher PLP and higher urinary PEA than heterozygous carriers, correlating with more severe disease [34]. Mornet and colleagues classified ALPL variants by dominant-negative effect and severity, finding that a large proportion of adults are heterozygous for variants without a demonstrable dominant-negative effect (suggesting haploinsufficiency), and proposed a three-form nosology in which a mild dominant form, characterised by low ALP and non-specific signs, is the form most often encountered in adults presenting with stress fractures or musculoskeletal pain [53]. Jandl and colleagues took a complementary clinical-genetic approach in 72 adults, proposing that in the presence of a rare likely pathogenic or pathogenic ALPL variant (American College of Medical Genetics and Genomics [ACMG] class 4 or higher) the diagnosis of adult HPP should require an associated bone complication, at least one additional complication involving teeth, muscle or the central nervous/mental system, repeated low TNSALP activity and elevated PLP [54].

3.4.3. IWG diagnostic criteria and diagnostic delay

The International HPP Working Group developed proposed diagnostic criteria for adults from a literature-surveillance review and a pooled prevalence analysis of candidate diagnostic characteristics, defining major and minor criteria and proposing diagnosis when two major criteria, or one major and two minor criteria, are present [55,56]. Recurrent metatarsal fractures and atypical femoral lesions or pseudofractures, together with a pathogenic/likely-pathogenic ALPL variant and elevated natural substrates, sit among the major criteria, with poorly healing fractures, chronic musculoskeletal pain, premature atraumatic tooth loss, chondrocalcinosis and nephrocalcinosis among the minor criteria [55,56]; companion paediatric criteria place adult HPP within a lifespan framework [38,57]. Diagnostic delay is a recurring theme: registry data show a delay of approximately 5-10 years, the Högler analysis approximately ten years, and the

UK rheumatology series 13 years [31,46,56]. Practical reviews emphasise that these delays converge on a single message, in non-specialised settings, including general sports medicine, the interval between first manifestation and HPP diagnosis is measured in years [15,58,59,60].

3.4.4. Pre-analytic and analytic pitfalls

Low ALP is not synonymous with HPP, and several pitfalls must be considered. Recognised secondary causes include hypothyroidism, hypercortisolism, severe malnutrition, vitamin B12, zinc or magnesium deficiency, coeliac disease, Wilson's disease, multiple myeloma, milk-alkali syndrome and antiresorptive therapy [19,55,61]. Acute fractures may transiently raise ALP and normalise the value in mild HPP, so a normal ALP measured immediately after a fracture does not exclude the diagnosis; oral contraceptive pills reduce bone-specific ALP; vitamin B6 supplementation can falsely elevate PLP and must be withheld for approximately one week before measurement; and PEA is a less sensitive, age- and diet-dependent supportive marker [9,10,15,16,17,18]. ALPL sequencing is the confirmatory test, but false-negative results occur in a small minority of clinically and biochemically established cases [34]. Belkhouribchia and colleagues similarly emphasised that adult HPP presenting as osteomalacia with low ALP is easily missed, exposing patients to inappropriate antiresorptive treatment and denying them family screening [61].

3.4.5. Differential diagnosis in the active patient

In athletes the differential diagnosis of recurrent stress fractures usually begins with training overload and progresses to REDs and the Female Athlete Triad, vitamin D deficiency, osteopenia/osteoporosis, osteomalacia, eating disorders and endocrine causes (thyroid, parathyroid, hypogonadism), with tumour-induced osteomalacia, multiple myeloma, primary hyperparathyroidism, Cushing's syndrome, osteogenesis imperfecta tarda and renal phosphate wasting also considered [1,2,3,4,16,17,18]. HPP belongs on this list whenever ALP is low, when stress fractures are recurrent or atypically located (multiple metatarsals, subtrochanteric femur, ulna in an archer), when fractures are disproportionate to training load or fail to heal despite adequate management, or when the childhood history reveals premature dental loss, delayed walking or "growing pains." The Female Athlete Triad and REDs are especially important comparators because they are common and clinically plausible and overlap with stress fractures, menstrual history, body composition and nutrition; yet the Fink case shows that this overlap can postpone rather than exclude an HPP diagnosis [2,3,4,17]. A structured differential framework is presented in Table 5.

3.5. PLP / vitamin B6 and mineral metabolism in adult HPP

3.5.1. PLP / B6 as a substrate marker rather than a therapeutic target

PLP is the principal circulating active form of vitamin B6 and a natural substrate of TNSALP. Because albumin-bound PLP cannot cross cell membranes, the membrane-bound enzyme must dephosphorylate circulating PLP to pyridoxal (PL), which crosses the cell membrane and the blood-brain barrier before being re-phosphorylated intracellularly to act as a cofactor for neurotransmitter synthesis. In HPP, deficient extracellular hydrolysis of PLP leads to extracellular PLP accumulation while reducing intracellular and central-nervous-system availability of pyridoxal, which in life-threatening infantile disease produces vitamin B6-dependent seizures [8,9,22]. Whyte and colleagues established markedly increased plasma PLP as the biochemical hallmark of HPP, and their later analysis of plasma pyridoxal (PL) and pyridoxic acid (PA) in 150 children and adolescents with HPP showed that PL in children was nearly twice that of healthy controls (66.7 vs 37.1 nM, $P<0.0001$) with unchanged pyridoxic acid, whereas affected adults often had PL and PA levels suggestive of dietary B6 insufficiency rather than excess [9,22].

Akiyama and colleagues extended this analysis to more than 100 HPP cases, showing that serum PLP, the PLP-to-PL ratio and the PLP-to-PA ratio are all higher in untreated HPP than in non-HPP patients and reflect clinical severity, that combining the PLP-to-PL ratio with PLP improves diagnostic sensitivity (especially in patients on B6 supplementation), and that enzyme replacement therapy is most clearly captured by a reduction in the PLP-to-PL ratio; cerebrospinal-fluid data supported a role for TNSALP in vitamin B6 transport across the blood-CSF barrier [20]. Alvarez and colleagues proposed a short vitamin B6 challenge as a diagnostic tool: after two days of pyridoxine, carriers of pathogenic ALPL variants showed a substantially higher rise in plasma PLP than non-carriers, with about one-third of carriers having a baseline PLP within the normal range, echoing the Christidis case and confirming that a single normal PLP does not exclude HPP [21,26]. Importantly, the empirical use of pyridoxine produced no symptomatic relief in four adults without seizures [34]. PLP and the broader B6-vitamer panel are therefore valuable as diagnostic and pathophysiologic biomarkers, and for monitoring the response to enzyme replacement therapy, but are not a therapeutic target in adult HPP outside the seizure phenotype.

3.5.2. Phosphate, calcium and the mineral milieu

Two studies by Kuehn and colleagues examined mineral intake in adults with HPP. The cross-sectional matched-pairs study compared 20 HPP patients with 20 matched controls using

detailed diet diaries: median phosphorus and calcium intake was lower in HPP patients (partly attributable to lower energy intake), and both high (≥1,375 mg/day) and low (<1,100 mg/day) phosphorus intake were associated with more frequent neuropsychiatric symptoms (P=0.02), while very high or very low calcium intake was associated with musculoskeletal, gastrointestinal and neuropsychiatric symptoms [62]. A subsequent intervention with a restricted-phosphorus, calcium-adjusted diet reported significant improvements in gait speed, chair-rise test and SF-36 vitality, but no significant change in 6-minute walk distance, overall pain or fatigue, leading the authors to conclude that overall clinical effectiveness on major issues remains limited [63]. These findings are observational and exploratory and support cautious, individualised dietary review rather than a generalised low-phosphorus prescription; for athletes with high training-induced energy demands the practical priority remains to avoid undernutrition and energy deficit, both of which independently raise stress-fracture risk.

3.5.3. Vitamin D, zinc and other micronutrients

Vitamin D and zinc deficiency are frequent comorbidities in adult HPP and are amenable to standard supplementation. Wiedemann and colleagues reviewed patients with suspected HPP at a specialised bone clinic; in the analytic subcohort (ACMG class 3-5 variants), vitamin D deficiency and zinc deficiency were common, and supplementation according to general guidelines significantly raised serum levels of the respective micronutrients without affecting ALP, PLP, phosphate, calcium, parathyroid hormone, bone-specific ALP, creatinine or desoxypyridinoline [64]. Because zinc and magnesium are catalytic cofactors of TNSALP, even minor deficiencies can further reduce residual enzyme activity and simulate or exacerbate HPP [55]. The authors concluded that general guidelines for vitamin D and zinc repletion apply to HPP patients without exacerbating the disease, and the broader principle of optimising bone health in inborn errors of metabolism applies equally to HPP [65]. This is directly relevant to athletes, in whom vitamin D insufficiency is common and independently associated with stress-fracture risk: vitamin D and zinc status should be assessed and corrected as in any other patient with a metabolic bone disorder, while empirical megadose vitamin therapy is not justified. The principal PLP/B6 and mineral-metabolism evidence is summarised in Table 4.

Table 4. PLP / vitamin B6 and mineral-metabolism evidence.

Source	Topic / design	Key verified facts	Practical message
Whyte et al. [9]	Foundational biochemistry	Established markedly elevated plasma PLP as the biochemical hallmark	PLP is the primary substrate marker of

		of HPP; PA unremarkable	low TNSALP activity
Millán & Whyte [8]	TNSALP biology (review)	PPi, PLP and PEA are the principal TNSALP substrates; mechanistic foundation	Explains the substrate logic of HPP
Whyte et al. [22]	B6 vitamers; 150 children + 13 adults	Children: PL roughly twice control (66.7 vs 37.1 nM, P<0.0001), PA unchanged; adults often show dietary B6 insufficiency	B6 status cannot be inferred from PLP alone; adult B6 insufficiency possible
Akiyama et al. [20]	>100 HPP cases; B6 vitamers	PLP, PLP-to-PL and PLP-to-PA ratios higher in untreated HPP and reflect severity; ratio + PLP improves sensitivity; ERT lowers PLP-to-PL	PLP is diagnostic and a treatment-monitoring marker, not a target
Alvarez et al. [21]	2-day vitamin B6 challenge	Carriers show a higher, more persistent PLP rise than non-carriers; ~1/3 of carriers have normal baseline PLP	Useful adjunct when baseline PLP is non-diagnostic but suspicion is high
Kuehn et al. [62]	Cross-sectional matched-pairs nutrition; 20 HPP + 20 controls	High (≥1,375 mg/d) and low (<1,100 mg/d) phosphorus associated with more neuropsychiatric symptoms (P=0.02); calcium extremes associated with more MSK/GI/neuropsychiatric symptoms	Dietary mineral balance modulates symptoms (observational)
Kuehn et al. [63]	Restricted-phosphorus, Ca-adjusted diet	Significant gains in gait speed, chair-rise test and SF-36 vitality; no significant change in 6MWT, overall pain or fatigue; authors conclude overall effectiveness on major issues remains limited	Supports individualised dietary review, not a generalised prescription

Wiedemann et al. [64]	Retrospective Zn / vitamin D supplementation	Frequent vitamin D and zinc deficiency; supplementation raised serum levels without changing ALP, PLP, phosphate, calcium, PTH, BAP	Correct standard deficiencies; this is not disease-specific HPP therapy
Lefever et al. [34]	Empirical pyridoxine in 4 non-seizure adults	No symptomatic benefit	Empirical B6 is not indicated for non-seizure adult HPP

Notes: BAP = bone-specific alkaline phosphatase; ERT = enzyme replacement therapy; GI = gastrointestinal; MSK = musculoskeletal; PA = 4-pyridoxic acid; PL = pyridoxal; PLP = pyridoxal-5'-phosphate; PPi = inorganic pyrophosphate; PTH = parathyroid hormone.

3.6. Treatment and functional implications in athletes with HPP

3.6.1. Enzyme replacement therapy (asfotase alfa)

Asfotase alfa is a bone-targeted recombinant human TNSALP, the first-in-class enzyme replacement therapy for HPP since its multinational approval in 2015, comprising the TNSALP catalytic domain, an IgG1 Fc domain and a deca-aspartate tail with high affinity for hydroxyapatite [39,66]. In a five-year study of adults and adolescents with HPP, treatment produced sustained reductions in PLP and PPi and functional improvement: median 6-minute walk distance rose from 355 m (range 10-620; n=19) before treatment to 450 m (range 280-707; n=13) at five years ($P<0.05$), with improvements in muscle strength and gross motor function, and injection-site reactions among the commonest adverse effects [28]. Its formal indications are jurisdiction-dependent and generally focus on paediatric-onset disease, although some jurisdictions permit use in adult-onset HPP, and recent reviews emphasise that adults regardless of age of onset can show meaningful improvement [30,67]. Across the primary athlete evidence, asfotase alfa was used in several adult and adolescent runners or a gymnast with healing of pseudofractures and return to running or other activity [16,17,18,23]; in an adolescent girl with HPP-related delayed union of a metatarsal stress fracture, AA also led to full radiological consolidation [24]. Improvements in physical function and health-related quality of life on asfotase alfa have also been documented in adults treated for paediatric-onset HPP, and longitudinal biomarker monitoring (including circulating microRNAs) illustrates the type of multimodal follow-up that may eventually inform individualised therapy [68,69]. No controlled trial has compared return-to-sport outcomes on versus off enzyme replacement therapy.

3.6.2. Teriparatide and other anabolic agents

Teriparatide (PTH 1-34) has been used off-label in adult HPP to stimulate osteoblast activity and promote fracture healing, with variable but sometimes meaningful improvement in healing, BMD and ALP that is often not sustained [13,15]. Al-Saoudi and colleagues reported complete bilateral healing of proximal femoral pseudofractures after 18 months of teriparatide in a 59-year-old man with paediatric-onset HPP, and Christidis and colleagues recommended a two-year course of teriparatide in their 35-year-old patient [26,49]. Because teriparatide is not approved for HPP, it is used pragmatically in selected patients in whom enzyme replacement therapy is unavailable or inappropriate, with short courses preferred [13,49]. Anti-sclerostin antibody therapy (BPS804/setrusumab) improved bone mineral density and bone-formation activity in a phase 2 study of adults with HPP [30].

3.6.3. Antiresorptive agents are contraindicated

Bisphosphonates and denosumab are contraindicated in HPP. Bisphosphonates are structural analogues of pyrophosphate; in a disease defined by extracellular PPi accumulation, antiresorptive therapy further suppresses an already deficient TNSALP activity, can worsen the underlying mineralisation defect and has been associated with atypical femoral fractures in unrecognised HPP [33,34,35,36,39]. In a physically active adult with recurrent stress fractures, low ALP and a presumed osteoporosis diagnosis, antiresorptive therapy should be deferred until HPP has been excluded.

3.6.4. Supportive, multidisciplinary management and functional outcomes

Beyond pharmacology, management of HPP in active patients involves optimisation of energy intake and nutritional status; correction of vitamin D and zinc deficiency where present; dental and periodontal care; physiotherapy and occupational therapy for pain, gait and function; psychological support for the anxiety/depression burden; and graduated, individualised return-to-sport protocols with attention to training load, footwear, running mechanics and the avoidance of sudden increases in volume or impact [1,42,43,64]. Low-impact alternatives such as cycling and swimming are useful during recovery [16]. In the published cases, individualised management permitted at least partial return to activity in several patients: the female runner returned to 5 km runs on asfotase alfa [18], the cross-country runner completed her season on enzyme replacement therapy and energy repletion [17], and the adolescent achieved radiological healing of the non-united fracture after asfotase alfa [24], while the runner who developed an allergic reaction illustrates the limits of enzyme replacement therapy [16]. These

case-level outcomes are encouraging but should not be generalised, since randomised or controlled return-to-sport data in HPP do not yet exist.

Table 5. Differential-diagnostic framework for an active individual with recurrent stress fractures and (low) ALP.

Condition	**Distinguishing features**	**Suggested initial work-up**
Hypophosphatasia (HPP)	Persistently low age- and sex-adjusted ALP; recurrent metatarsal and/or subtrochanteric/diaphyseal femoral fractures; elevated PLP/B6 in most (not all) cases; ALPL variant; childhood dental issues or "growing pains"	Repeat ALP (including historical values); exclude secondary causes; plasma PLP/vitamin B6 (off B6 supplement ≥1 week); consider 2-day B6 challenge; ALPL sequencing; urinary PEA where available
REDs / Female Athlete Triad	Low energy availability or weight loss; menstrual dysfunction; low/decreased BMD-for-age; predominantly endurance, aesthetic and weight-class sports; can coexist with HPP	Energy-availability and menstrual history; eating-behaviour assessment; DXA; hormonal panel; 25-OH-vitamin D; ferritin; nutrition referral; include ALP and B6 in the panel
Vitamin D deficiency / osteomalacia	Low 25-OH-vitamin D; bone pain; muscle weakness; ALP usually elevated in classic osteomalacia (low in HPP)	25-OH-vitamin D; calcium, phosphate, PTH; ALP (note: osteomalacia with low ALP can also occur)
Premature / secondary osteoporosis	Reduced BMD; fragility fracture; secondary causes (glucocorticoids, hypogonadism, hyperthyroidism, coeliac disease)	DXA; secondary-cause panel; vitamin D; PTH; TSH; coeliac serology; check ALP, avoid empirical bisphosphonates if ALP low
Bisphosphonate-associated AFF	Long-term bisphosphonate or denosumab; transverse lateral-cortex fracture; bilateral in a substantial minority; HPP-related AFFs can mimic and occur after exposure in unrecognised HPP	Detailed drug history; baseline ALP before antiresorptives; bilateral imaging; ALP/PLP and ALPL if low ALP coexists

Rheumatic disease, fibromyalgia, chronic fatigue	Diffuse pain; tender points; rheumatic disease has serology; HPP can present as CPPD/chondrocalcinosis or pseudo-gout	Inflammatory markers; ANA/RF; serum ALP (do not skip); 25-OH-vitamin D; ferritin; TSH; consider HPP if ALP persistently low
Osteogenesis imperfecta tarda	Childhood fractures; blue sclerae; hearing loss; collagen-related variants	Family history; ALP typically normal/elevated; collagen-gene panel
Other causes of low ALP	Hypothyroidism, hypercortisolism, malnutrition, zinc/magnesium or B12 deficiency, Wilson disease, multiple myeloma, milk-alkali, antiresorptive use	TSH, cortisol; zinc, magnesium, B12; ceruloplasmin; serum/urine protein electrophoresis (SPEP/UPEP); review medications and sample handling

Notes: AFF = atypical femoral fracture; ALP = alkaline phosphatase; BMD = bone mineral density; CPPD = calcium pyrophosphate deposition disease; DXA = dual-energy X-ray absorptiometry; PEA = phosphoethanolamine; PLP = pyridoxal-5'-phosphate; PTH = parathyroid hormone; REDs = Relative Energy Deficiency in Sport; TSH = thyroid-stimulating hormone. Synthesised from references [2,3,4,13,14,19,29,31,33,34,35,39,55,61]; this table is a clinical differential-diagnostic framework rather than a tabulation of individual studies.

4. Discussion

The literature reviewed here, although limited in volume, is internally consistent in showing that HPP can present in adult athletes and physically active individuals as recurrent stress fractures, with or without features classically attributed to overtraining, REDs or the Female Athlete Triad. Six interpretive theses follow, each grounded in the verified evidence summarised in Section 3.

4.1. HPP in athletes is rare but clinically important

Direct evidence is restricted to a small set of case reports and a single case-finding study [16,17,18,23,24,25,26,27]. Despite this small base, the cases converge on a recognisable phenotype: recurrent metatarsal or femoral stress fractures, often without major trauma; delayed healing; persistently low age- and sex-adjusted serum ALP, sometimes undetectable; elevated PLP/vitamin B6 in most though not all confirmed cases; childhood signs recognised only in hindsight (dental problems, "growing pains," delayed motor milestones); and a pathogenic or likely-pathogenic ALPL variant. The phenotype is reproducible across endurance running,

gymnastics, archery and recreational activity, and in both sexes. The absolute number of cases is small because HPP itself is rare, but the diagnostic and therapeutic consequences, avoidance of contraindicated antiresorptives and access to enzyme replacement therapy, are substantial.

4.2. Recurrent or atypical stress fractures should trigger ALP measurement

Stress fractures of the metatarsals, subtrochanteric femur, ulna or other non-canonical sites, particularly when injury seems disproportionate to training load or when fractures recur despite adequate management and graded return-to-play, justify checking serum ALP [16,17,18,25,26,27]. The cost is negligible and, in this enriched population, the diagnostic yield is meaningful: among adults with metatarsal stress fracture and low ALP, 2 of 13 (15%) carried a pathogenic ALPL variant [27]. Recurrent metatarsal fractures and femoral pseudofractures also feature among the proposed adult diagnostic criteria, so they are not marginal findings but part of the diagnostic core [55].

4.3. HPP can be masked by, and can coexist with, more common diagnoses

The Fink case is paradigmatic: a Division-I cross-country runner met clinical criteria for the Female Athlete Triad yet had undetectable ALP, elevated B6 and a confirmed ALPL variant [17]. The Triad and REDs frameworks direct clinicians toward energy availability, menstrual function and BMD, none of which captures HPP [2,3,4]. Conversely, adult-onset HPP is misdiagnosed as osteoporosis, fibromyalgia, chronic fatigue syndrome, rheumatic disease or simple overuse [19,34,46,56]. In athletes, a working diagnosis of overuse, REDs or the Female Athlete Triad does not exclude HPP, and an established Triad diagnosis should not delay measurement of ALP when fractures recur or heal poorly.

4.4. BMD is not a reliable surrogate, and diagnostic delay is the modifiable harm

Hepp's controlled cohort showed more non-vertebral low-energy fractures in HPP than in matched controls without any difference in BMD, and Genest's cohort found that lower ALP and higher PLP/PEA correlated with higher rather than lower lumbar-spine T-scores, with higher lumbar BMD paradoxically associated with increased fracture risk [40,41]. A normal or above-normal lumbar DXA therefore should not be used to rule out HPP, and impaired bone-matrix organisation may contribute to fragility despite preserved BMD [32]. Diagnostic delay, approximately 5-10 years in registries and a median of 13 years in general rheumatology, is the principal modifiable harm, because affected adults accumulate fractures, functional and psychological burden, and the risk of inappropriate antiresorptive treatment [31,34,46,56]. Reducing it requires only that ALP be measured and interpreted against its lower limit, that

PLP be tested when ALP is low, and that ALPL testing be available for confirmation [6,7,21,27].

4.5. PLP and B6 vitamers are biomarkers, not therapeutic targets in adult HPP

PLP is the most sensitive substrate biomarker, reflects clinical severity and is essential when ALP is low or borderline [9,20,22]; the PLP-to-PL ratio improves diagnostic performance and best captures the response to enzyme replacement therapy [20]. The 2-day B6 challenge is a useful adjunct when baseline PLP is non-diagnostic but suspicion is high [21]. By contrast, the therapeutic value of B6 supplementation in adult HPP is not established: empirical pyridoxine produced no symptomatic relief in four adults without seizures [34]. Athletes diagnosed with HPP should therefore receive individualised nutritional counselling rather than empirical megadose vitamin therapy, and should avoid antiresorptive agents [34,35].

4.6. Background literature is essential but must not be over-interpreted

Adult-HPP cohorts and reviews, low-ALP and diagnostic-criteria publications, and the REDs/Female Athlete Triad consensus statements are indispensable for interpreting athlete cases, but none of them is direct evidence about HPP in athletes. That adult-HPP studies show metatarsal fractures supports the plausibility of HPP in a runner with metatarsal fracture; it does not establish prevalence or risk in athletic populations. This distinction is methodologically important and has been preserved throughout this review. Taken together, the evidence supports a pragmatic algorithm for the active patient with recurrent or atypical stress fractures: measure ALP and obtain historical values; if ALP is low, measure PLP/vitamin B6 (withdrawing B6 supplements for one week) and consider PEA and ALPL sequencing; screen for the Female Athlete Triad and REDs in parallel rather than as alternatives; avoid bisphosphonates until HPP is excluded; refer to a metabolic-bone specialist and genetic counsellor when low ALP is unexplained; individualise return to sport; and, in selected patients, consider enzyme replacement therapy or anabolic agents, recognising that adult-onset indications are not fully defined [16,17,18,19,28,55,67].

5. Limitations

This review has several limitations. First, the volume of primary evidence on HPP in athletes and physically active individuals is small and is restricted to case reports and a single case-finding study, which constrains generalisation to specific sports, age groups or sex. Second, three of the primary cases describe adolescents and young adults (16-20 years); although their athletic context is explicit, adolescent metabolic bone biology differs substantially from that of

adults in their thirties and forties, and their treatment responses and fracture-healing trajectories should not be extrapolated directly to mid-life adult-onset HPP. Third, the contextual adult-HPP literature is heterogeneous, ranging from single-centre case series to national cohorts and multi-centre registries, without standardised reporting of fracture sites, biomarkers or treatment regimens, and ALP reference ranges are laboratory-specific. Fourth, parts of the supporting literature were identified through Google Scholar Labs, hand-searching and citation chasing rather than the primary database query; this is methodologically transparent but is acknowledged as a non-systematic component of evidence retrieval. Fifth, consensus references (diagnostic criteria, REDs and Female Athlete Triad statements, foundational PLP/B6 biochemistry) are used for framing, not as direct evidence of HPP behaviour in athletes. Sixth, quantitative figures in the synthesis were extracted from and verified against the full text of the source papers, and where a paper's full text did not specify an exact figure the claim was kept at a general level rather than assigning a precise value. Seventh, the review was restricted to English-language sources. Finally, no quantitative meta-analysis was performed, and effect estimates from the primary evidence are descriptive only.

6. Conclusions

Although adult HPP is rare and the literature on HPP in athletes is small, the available primary-evidence case reports and one case-finding study consistently show that recurrent metatarsal or atypical stress fractures with a persistently low ALP, often accompanied by elevated PLP/vitamin B6, can be the presenting feature of HPP in runners, an archer and other active adults. The combination of recurrent stress fractures, disproportionate injury and a persistently low or low-normal ALP should not be attributed to overuse, REDs or the Female Athlete Triad until HPP has been actively considered and, where appropriate, excluded by PLP/B6 testing and ALPL sequencing. HPP and the Female Athlete Triad/REDs are not mutually exclusive and can coexist.

The contextual adult-HPP literature confirms that the typical fracture pattern, the substantial pain, fatigue and functional burden, the diagnostic delay measured in years and the risk of misdiagnosis as osteoporosis, fibromyalgia or rheumatic disease are all relevant to the active patient. BMD alone does not capture the fracture risk; ALP does. PLP and the broader B6 vitamer panel, with the 2-day B6 challenge as an adjunct, secure the biochemical phenotype, and ALPL testing confirms the diagnosis. Antiresorptive therapy should be avoided in any athlete with unexplained low ALP, given the documented risk of atypical femoral fractures in unrecognised adult HPP. Enzyme replacement therapy, anabolic agents such as teriparatide,

individualised nutrition and rehabilitation support at least partial return to activity in selected patients, but evidence in adult-onset HPP and in athletes specifically remains anecdotal. Greater awareness across sports medicine, endocrinology, orthopaedics, podiatry and rheumatology, together with prospective case-finding studies that capture athletic exposure and sport-specific outcomes, is needed to reduce diagnostic delay and improve outcomes.

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The authors report no specific disclosures relevant to this literature review.

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Conflicts of Interest

The authors declare no conflict of interest.

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