Review

Osteogenesis imperfecta, diffuse idiopathic skeletal hyperostosis, and hypophosphatasia: one year in review 2025

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ABSTRACT
There are several metabolic bone diseases that rheumatologists should be aware of in clinical practice. In this paper, we reviewed the literature published in 2024 on osteogenesis imperfecta, diffuse idiopathic skeletal hyperostosis, and hypophosphatasia.

Introduction
Rheumatologists should be able to recognise qualitative and quantitative alterations of the bone. Some bone diseases are characterised by skeletal fragility, *e.g.* osteogenesis imperfecta (OI) and hypophosphatasia (HPP). Others do not alter the mechanical competence of the skeleton but alter its conformation through processes of hyperostosis and/or osteosclerosis; the most common in this category is diffuse idiopathic skeletal hyperostosis (DISH). In this paper, which is part of a series of articles published annually as 'One Year in Review' (1, 2), we focused on the three aforementioned diseases for the following reasons: OI is gradually acquiring a precise connotation in terms of classification, aetiology, and clinical picture; the first HPP diagnostic criteria for both adults and juveniles were recently proposed; DISH deserves special attention, as it is not the clinically benign and incidental radiological finding we previously used to know.

Osteogenesis imperfecta
Osteogenesis imperfecta (OI), or 'brittle bone disease', is a group of rare hereditary disorders characterised by recurrent fragility fractures and/or bone deformities. It has a wide range of severity, from mild to death *in utero*. OI is mainly caused by mutations altering the quantity, structure, post-translational modification, or cross-linking of type I collagen, which constitutes up to 90% of the extracellular bone matrix. The *COL1A1* and *COL1A2* genes, which encode for the α1 and α2 chains of the type I collagen heterotrimer, are affected in more than 90% of Caucasian cases. Other less common mutations affect bone mineralisation or osteoblastogenesis. Depending on the affected gene, extraskeletal manifestations may occur with variable frequency, such as joint hypermobility, short stature, and others related to the cardiovascular, visual, auditory, and pulmonary systems. Both genders are equally affected, with an incidence of 1:10,000 individuals. Age at presentation ranges from the prenatal period to childhood or adolescence. Diagnosis relies on clinical examination, imaging, and genetic testing. Management varies according to the manifestations of each patient (3).

Have we achieved a satisfactory classification of OI?
In 1979, before any genetic basis for OI was known, four different OI types with differing clinical manifestations and disease severity were established and labelled with Roman numerals: 'Dominantly inherited non-deforming with blue sclerae' (Type I), 'Perinatally Lethal' (Type II), 'Progressively deforming' (Type III), and 'Dominantly inherited with normal sclerae' (Type IV) (4). Later, a fifth type was added (Type V), characterised by calcification of forearm interosseous membranes, high risk of hyperplastic callus after fracture or surgery, and coarse mesh-like lamellation on histomorphometry. More recently, Arabic numerals have replaced Roman numerals to refer to Sillence phenotypes (types 1-5), which are currently defined as follows:
- Type 1: increased bone fragility, blue or greyish sclerae, no bone deformities.

- Type 2: prenatal fractures of ribs and long bones, death in utero or shortly after birth.
- Type 3: severe bone fragility, progressive skeletal deformities, normal sclerae.
- Type 4: moderate bone fragility, variable bone deformities, normal sclerae.
- Type 5: moderate to severe bone fragility, progressive calcification of forearm interosseous membranes, hyperplastic callus at the site of bone trauma/fracture (5).

Following the gradual discovery of an array of genes responsible for OI pathogenesis since the 2000s, both identification codes and progressive Roman numerals were used to catalogue various OI types, each caused by mutations in a distinct gene locus. To date, 23 OI types (I-XXIII) are listed in the *Online Mendelian Inheritance in Man* (OMIM) database. Each of these is then grouped under one or more Sillence phenotypes, as applicable in accordance with the range of clinical manifestations and the severity resulting from mutations in the affected gene locus. As a result, the current OI classification is based on a dyadic nosology (6) (Table I).

A recent review (7) collected the newest evidence on OI genetics and pathophysiology. The authors grouped all genomic OI types according to the underlying pathophysiological mechanisms. Types I-IV are caused by mutations of *COL1A1* and *COL1A2* genes, resulting in altered type I collagen quantity (type I) or structure (types II-IV) and in a variable degree of phenotype severity (Sillence phenotypes 1 to 4). Other pathophysiological mechanisms include altered bone mineralisation (types V-VI), abnormal type I collagen post-translational modification (types VII-IX), altered type I collagen processing and cross-linking (types X, XI, XIII, and XXI), altered osteoblast differentiation and function (types XII, XIV-XVIII), defects in the bone morphogenetic protein / transforming growth factor-b (BMP/TGF-b) pathway (type XIX), decreased low-density lipoprotein receptor-related protein 5/6 signalling (type XX), and dysregulated mitogen-activated protein kinase/

extracellular signal-regulated kinase (MAPK/ERK) pathway (type XXII) (7). Type XXIII is linked to modifications of insulin-dependent Akt phosphorylation with consequent defects of type I collagen synthesis (8).

OI classification is often a matter of debate (9). Some investigators recently claimed that OI classification should be primarily based on genetics because this approach may facilitate preconception counseling and may not be complicated by the phenotypical heterogeneity of OI. Indeed, disease phenotype of a patient with OI may evolve over time, thereby causing shifts to a different Sillence type from baseline, and it has been previously noted that individuals within the same family and carrying the same mutation may display different clinical manifestations and thus may be classified with different OI types

(7). However, the currently accepted approach, as recently published (6), is the use of a combination of both genotyping and phenotyping in OI nosology (Table I). Adding a phenotypical aspect to OI classification may provide with insights into the probable course of a given OI type and may facilitate the evaluation of treatment efficacy in future studies (5). The classification of OI based on genetic variants may expand as new genetically determined mechanisms are discovered.

Clinical manifestations of OI: what is new?

Rare diseases are often underinvestigated, resulting in persistent unawareness and in diagnostic and/or therapeutic delays to patients which may represent as much as 10% of the general population (10). Unfortunately, OI is

Table I. Dyadic nosology for OI (6).

Sillence Classification (type)	Gene	Mode of inheritance	OMIM number	OMIM type
1	COL1A1	AD	166200	I
	COL1A2	AD	166200	I
	PHLDB1	AR	620639	XXIII
2	COL1A1	AD	166210	II
	COL1A2	AD or AR	259400	II
2 or 3	P3H1	AR	610915	VIII
2, 3 or 4	CRTAP	AR	610854	VII
	PPIB	AR	259440	IX
3	COL1A1	AD or AR	259420	III
	COL1A2	AD or AR	259420	III
	SERPINF1	AR	613982	VI
	SERPINH1	AR	613848	X
	BMP1	AR	614856	XIII
	TMEM38B	AR	615066	XIV
	WNT1	AR	615220	XV
	CREB3L1	AR	616229	XVI
	SPARC	AR	616507	XVII
	TENT5A	AR	617952	XVIII
	MESD	AR	616294	XX
	KDELR2	AR	619131	XXI
	CCDC134	AR	619795	XXII
3 or 4	FKBP10	AR	610968	XI
	SP7/OSX	AR	606633	XII
	MBTPS2	XLR	301014	XIX
4	COL1A1	AD	166220	IV
	COL1A2	AD	166220	IV
	PLOD2*	AR	609220	NA
5	IFITM5	AD	610967	V

*PLOD2 mutations cause Bruck syndrome type 2 (OI with congenital joint contractures).
AD: autosomal dominant; AR: autosomal recessive; XLR: X-linked recessive; NA: not applicable.

no exception. We collected the latest evidence published in 2024 related to clinical manifestations of OI, giving priority to large patient cohorts and systematic reviews.

The largest Italian OI cohort, featuring an equal distribution between juveniles and adults, was recently described (11). The Sillence Classification was employed to classify 568 subjects as unknown type (29.2%), type I (54.6%), type III (5.5%), type IV (10.4%), or type V (0.3%). Most of their findings were in line with the previous literature. The height was considerably lower in types III, IV and V, with mean Z-scores of -4.89, -2.77, and -2.74, respectively, compared to the general Italian population; by contrast, type I OI patients had a mean Z-score of -0.89. Approximately half of the cohort had at least one deformity involving the trunk (45.6%), the lower (15.5%) or upper limbs (5.8%). Facial dysmorphisms (frontal bossing, prognathism, triangular face), which had been previously underinvestigated, were present in 21% of cases. Fractures occurred in 495 (87%) patients, whereas the prevalence of osteoporosis (25.5%) and osteopenia (13.9%) on dual-energy x-ray absorptiometry (DXA) was lower and mostly affecting types III and IV. Joint hypermotility was present in 38.2% of patients and equally among types. Despite the clinical evidence of OI, a mutation was not found in 23.1% of patients. The *COL1A1* (71.6%) and *COL1A2* (25.6%) genes were most affected.

Research on OI has been mostly focused on juvenile patients. To prompt future studies, a recent review (12) highlighted knowledge gaps related to menopause and estrogen deficiency, fertility rate and pregnancy outcomes, neurologic complications (*e.g.* which patients should be screened for basilar invaginations or intracranial aneurysms), the prevalence of gastrointestinal manifestations and joint hypermobility, and the effects of aging on vision, hearing and dentition in OI patients.

A systematic review (13) focused on cardiovascular complications in OI. While echocardiograms may show larger aortic roots more often in OI patients than in controls, it is unknown whether

they worsen over time. Furthermore, while valvular regurgitation was found to be significantly more prevalent in OI patients, whether specific OI types or heart valves are affected more often than others is unknown (13). A Chinese cross-sectional study (14) on 48 OI patients (type I, 60%) found mild mitral and tricuspid valve regurgitations with a prevalence of 12% and 36%, respectively, in 25 juveniles, and of 13% and 17%, respectively, in 23 adults; moreover, abnormal echocardiograms were significantly more frequent in juveniles with joint hypermobility. However, the sample size was too small to draw any definitive conclusions (14). In summary, no guidelines on whether or how to screen and/or monitor OI patients for cardiovascular complications are currently available (12, 13), but it is reasonable to perform echocardiograms at baseline for all patients, especially when joint hypermobility is present (14). Prospective studies on cardiovascular complications are needed.

A recent systematic review (15) focused on dental abnormalities in OI. The authors confirmed that these are especially common in OI types III-IV, caused by type I collagen qualitative defects. Dentinogenesis imperfecta (DI) type I, a condition caused by altered dentin formation and resulting in fragile teeth with frequent yellow-brown discoloration, was shown to have a prevalence of 20–48% in OI. Concerning malocclusions, it was found that class III (prognathism) is the most common in OI with a prevalence between 4.1% and 84%, as opposed to the general population in which it is the least common. In summary, although no prospective studies with appropriate dental examinations have been published yet, regular dental care is recommended for OI patients, especially as dentin problems may be missed on inspection only (15).

Hearing loss (HL) can be caused by fractures or atrophy of the bones in the middle ear in type 2 OI (conductive HL), by otosclerotic lesions with extension into the inner ear in non-type 2 OI (conductive and sensorineural HL), or primary degeneration of the cochlear structure (sensorineural HL) (3). A nationwide Danish register-based cohort

study (16) on 864 OI patients and 4276 controls followed up over a mean period of approximately 28 years found that HL was significantly more prevalent (17% *vs*. 4%, respectively) and precocious (median age at diagnosis 42 *vs*. 58 years, respectively) in the OI group. Moreover, hearing aids were more frequent in OI patients (12.5% *vs*. 3%) and were needed at a median age of 45 vs 60 years, respectively. Although it was not possible to correlate OI types with the occurrence of HL and data regarding the type of hearing loss were not available in all cases, the authors reported that half of the OI cohort suffered from HL by age 75. Therefore, regular audiometric visits are highly recommended in OI patients (16). Unfortunately, hearing loss in OI seems to be unaffected by antifracture therapy.

Type I collagen is a major component of all structures in the eyes, *e.g.* the cornea, sclera, and retinal vessels; therefore, ocular complications, even vision-threatening ones, may occur in OI. However, a recent scoping review failed to retrieve enough literature evidence to formulate screening recommendations to identify patients at risk for ocular complications (17).

Blue sclera is a common manifestation of OI (3). Considering the absence of an objective method to detect it, Di Martino and colleagues proposed the 'BLUES' procedure (18). This consisted in the elaboration of photographs of patients' sclerae on the Adobe Photoshop software. Sclerae were defined as 'blue' when the percentage of the blue peak on the RGB colour curves was larger than or equal to 17%. When evaluating 124 eyes of OI patients and 70 eyes of healthy controls, the sensitivity and specificity of the 'BLUES' were 89% and 87%, respectively, and the diagnostic agreement with OI was comparable to that resulting from regular assessments by expert ophthalmologists (18). More studies are needed to validate this procedure which seemed easy and inexpensive.

Novelties in OI therapy

The recent, numerous advances in OI pathophysiology and molecular mechanisms have not been paralleled by the development of an equivalent num-

ber of OI-specific drugs. The current pharmacological approach is the use of anti-osteoporotic medications (AOMs), based on the assumption that these may be effective against the increased bone fragility observed in OI. Another significant problem is that AOMs have been mostly studied in juvenile OI patients and less extensively in adults (19). We reviewed the latest evidence on AOMs used in OI.

Bisphosphonates have been the most studied drugs in adults with OI and, despite the lack of guidelines, currently represent the cornerstone of OI therapy (20). Since 2003, there is evidence suggesting that intravenous infusions of 100 mg neridronate every 3 months can effectively improve bone mineral density (BMD) (21) and with a good long-term safety profile (22). Even though high cumulative doses of zoledronate may delay tooth eruption in OI juveniles (23), its efficacy at increasing BMD was demonstrated in a randomised controlled trial (RCT) (24). However, fracture risk reduction efficacy is not yet established as there are no RCTs from which solid data regarding bisphosphonates can be obtained (20).

The anti-RANKL monoclonal antibody denosumab may be an effective alternative in patients with chronic kidney disease or in case of bisphosphonate intolerance (20). A recent RCT (24) involving 51 adults with OI receiving either denosumab 60 mg every 6 months or one intravenous infusion of zoledronate 5 mg showed that both were equally effective at improving BMD and trabecular bone score (TBS) with no significant differences between the two treatments after 12 months and with more pronounced results in patients with quantitative type I collagen defects. The short duration of the study and the small sample size did not allow to conclude on fracture risk reduction. A better safety profile was observed with denosumab due to frequent acute-phase reactions with zoledronate (0% vs. 34.6%, respectively) (24). Another study (25) involving 84 juvenile OI patients compared denosumab (30 mg or 60 mg if age <5 years or >5 years, respectively, every 6 months) and zoledronate (2.5 mg or 5 mg if body weight

<25 kg or >25 kg, respectively) over 12 months. Although both treatments significantly increased BMD from baseline, increases at femoral neck and total hip BMD were significantly more pronounced with zoledronate. Safety was a concern in both groups: 30 (71%) of the patients treated with zoledronate developed acute-phase reactions (vs. 0% in the denosumab group), and 13 (31%) of those treated with denosumab suffered from rebound hypercalcaemia after a mean of 4.7 months from the last injection, with 6 of them having a hypercalcaemic crisis. The impact on fracture risk reduction could not be assessed due to the one-year duration of the study. It was concluded that denosumab is a valid second-line drug in OI juveniles, but careful monitoring of calcium levels is recommended (25).

Teriparatide, a human 1-34 parathyroid hormone (PTH) analogue, can effectively increase BMD in OI patients and can be employed in patients with a high fracture risk (20). The TOPAZ trial (NCT03735537) (26), in which 350 adult OI patients have been randomised to receive standard care or teriparatide for two years followed by one infusion of zoledronate, will reveal whether the latter strategy is able to reduce fracture risk. Abaloparatide, a PTH-related protein analogue, has not yet been studied in OI (20).

Romosozumab, an anti-sclerostin antibody, significantly increased BMD and improved bone microarchitecture (TBS) in a case report of two adults with OI (27). Although no RCTs on adults have been conducted yet, the results of a phase III study (NCT05972551) investigating its fracture risk reduction efficacy in OI children may be available in 2027 (20). The recently published results of the phase IIb of the ASTEROID study (28) found that setrusumab 20 mg/kg, another anti-sclerostin antibody, enhanced bone health by significantly increasing total and cortical volumetric BMD of tibia and radius, radial cortex thickness, and tibial stiffness in adults with OI types I/III/IV, with an overall good safety profile. After 12 months, lumbar spine, total hip and femoral neck BMD increased by a mean of 9%, 2.5% and 3.4%, respectively (28). Fol-

lowing these results, a phase III evaluation will be carried out.

Altered bone turnover in severe OI types may underlie excess levels of TGF-β. In 2022, a phase II RCT (29) showed that fresolimumab, an anti-TGF-b antibody, was safe in OI patients and increased spine BMD in type IV but not in patients with types III or VIII. Another drug with a similar mechanism, SAR439459, is under investigation in a phase Ib RCT on adults with OI types I or IV (20). At present, it is too early to draw any conclusions on the use of this type of drugs in OI.

A phase I/II open-label trial (30) will evaluate safety and efficacy of allogeneic cryopreserved expanded first trimester fetal mesenchymal stem cells (MSC) in infants and fetuses with OI types III and IV, based on previous knowledge that MSC transplantation led to engraftment in bone, enhanced collagen secretion and bone mineralisation in OI murine models.

Take-home messages
- A dyadic nosology of OI is currently in use. Twenty-three OI types with different genetic aetiologies are labelled with Roman numerals (I-XXIII) and are also grouped under phenotypic Sillence categories labelled with Arabic numerals (types 1-5) (6).
- Several knowledge gaps need to be addressed with regards to audiological (16), cardiovascular (13), ophthalmological (17), neurological, gynaecological, and gastrointestinal manifestations (12) of OI.
- Bisphosphonates, particularly neridronate and zoledronate, are the cornerstone of OI therapy (20). Denosumab is efficacious but should be used with caution in juveniles due to frequent rebound hypercalcaemia (25). More OI studies are needed on teriparatide, abaloparatide, romosozumab, and setrusumab (20). Anti-TGF-β antibodies (29) and MSC transplantation (30) are currently under investigation.

Diffuse idiopathic skeletal hyperostosis: beyond a radiological finding
DISH is a systemic disorder characterised by abnormal ossification involving

the spine and, less commonly, peripheral entheses at the shoulder, elbow, knee, and calcaneus. It was first described by Donald L. Forestier and Jaume Rotes-Querol in 1950 (31). The vertebral bodies are typically affected on their anterior right side in the thoracic region, and less commonly in the cervical or lumbar tract. The pulsating descending aorta may act as a protective mechanical barrier to the left side of the thoracic spine. DISH is often regarded as a mere incidental radiological finding; however, it may cause dysphagia, restrictive lung disease, back pain, radiculopathy, myelopathy, a limited spinal range of motion, and a higher risk of fragility fractures of the vertebrae (VFx) (32).

Several sets of classification criteria have been proposed for DISH, however with a lack of consensus for which is best to use, thereby hampering comparisons among different cohorts (33). The most frequently used set was defined by Resnick and Niwayama in 1976 (34); these criteria consist of three items: ossification of the anterolateral aspect of at least four consecutive vertebral bodies (≥3 bony bridges); relative intervertebral disc height preservation and the absence of extensive radiographic changes of "degenerative" disc disease, *e.g.* vertebral body marginal sclerosis; and the absence of zygoapophyseal ankylosis and inflammatory changes of the sacroiliac joints, such as sclerosis, erosion, or bony ankylosis. Oudkerk *et al.* (35) brought modifications to enhance interobserver agreement for the diagnosis of DISH by computed tomography (CT) scans, and Kuperus *et al.* (36) proposed a set to improve DISH detection at its early phase. The Mata score evaluates radiological progression at both spinal and peripheral sites (37).

Prevalence: insights from imaging studies

Although the prevalence of spinal DISH was initially evaluated with chest x-rays, more accurate studies using CT scans reported a prevalence of 19.5% in Japanese, 24.4% in Koreans, and 7.7% in African Americans (38). By contrast, data on the prevalence of extraspinal DISH are lacking.

A cross-sectional survey carried out in India in 2024 (38) investigated the prevalence of DISH as defined by the modified Resnick criteria (35). A total of 1815 polytrauma patients (1453 males), with a mean age of 47.5 years, performed a whole spine CT scan. The overall prevalence of DISH was 19.1% (n=347) and was higher in men (20.2%) than in women (14.9%); it correlated with obesity, diabetes mellitus, ischaemic heart disease, and increasing age, with the highest rate observed in individuals over 80 years old (45.5%) (38). Fournier *et al.* (39) conducted a retrospective analysis of thoracic spine CT scans performed by 1536 North American adults (50.1% males) to assess the prevalence of both established DISH and early-phase DISH. Established and early-phase DISH were found in 14.2% and 13.2% of individuals, respectively, both being more common in males (20.9% and 15.8%, respectively) than in females (7.4% and 10.4%, respectively). Notably, the study suggested that more than 30% of people over the age of 39 years may feature imaging findings compatible with early-phase or established DISH. An increase in DISH prevalence may occur in the future because of population aging (33).

DISH: a clue to metabolic and cardiovascular diseases

It is well known that DISH shows a significant association with metabolic disorders, such as diabetes mellitus, hyperinsulinaemia, obesity, dyslipidaemia, hyperuricaemia, metabolic syndrome, and obesity (40). To assess whether these risk factors increased the prevalence of DISH also in younger patients, Brikman *et al.* (41) retrospectively analysed chest and spine CT scans from 183 obese patients (median body mass index - BMI: 40.6 kg/m^2; range 35–73) with a mean age of 40.4 years (range 31–50). DISH was diagnosed in 33 (18%) patients, and other 8 (4.4%) subjects were classified as 'near-DISH', *i.e.* did not fulfill the criteria for established DISH but showed early signs of it. Patients with DISH were older, were more frequently smokers, and had a significantly higher rate of hypertension and obstructive sleep apnea. These findings

emphasise the importance of recognising DISH as a possible musculoskeletal complication of metabolic syndrome; furthermore, it would be interesting to assess whether an early and successful management of obesity prevents ossification.

Adami *et al.* (42) investigated the relationship between DISH and coronary artery disease (CAD) in 187 patients undergoing coronary angiography between 2016 and 2021. Approximately 44% of the cohort had a confirmed diagnosis of DISH according to Resnick criteria. Using the SYNTAX score-II, which is a score to predict clinical outcomes in patients with CAD analysing anatomic and clinical variables, patients with DISH showed higher scores than non-DISH patients (29.0±19.4 *vs.* 22.5±14.9, respectively), suggesting higher CAD severity. In regression analyses, the presence of DISH was linked to a significantly higher risk of complex CAD, independent of age, sex, BMI, and comorbidities. Furthermore, echocardiographic analysis revealed that DISH patients more frequently had valvular calcifications (30.1% *vs.* 12.5%). These findings suggest that DISH diagnosis in patients with CAD may warrant more intensive cardiovascular risk management.

From cytokines to calcifications: the evolving story of pathogenesis

The cause of bone formation in DISH is unclear, but several studies suggested that cytokines, growth factors, and adipokines may play a role acting both on enthesis and bone. Obesity and visceral fat are correlated with higher levels of proinflammatory cytokines, *e.g.* BMPs and insulin-like growth factor 1 (IGF-1) and 2 (IGF-2), and of adipokines, *e.g.* leptin and adiponectin. These may promote bone formation by inducing transformation of mesenchymal cells into fibroblasts and osteoblasts. In addition, a low-grade systemic inflammatory state may promote new bone formation, resembling the mechanism observed in spondyloarthritis (43). Indeed, proinflammatory cytokines acting at entheses both in DISH and spondyloarthritis may stimulate mesenchymal stem cells to differentiate

into osteoblasts promoting pathological ossification (44).

Littlejohn (45) summarised the most recent evidence regarding the sites of origin of new bone formation and growth factors potentially involved in DISH. Bone formation appears to be mediated by mesenchymal stem cells located in the outer fibrous layer of the enthesis and by undifferentiated skeletal stem cells residing within the peripheral zones of the annulus fibrosus and the bony eminences of vertebral bodies. These progenitor cells represent cellular targets for local growth factors which drive their differentiation into mature osteoblasts, ultimately promoting ossification within the axial skeleton. Growth factors involved in these processes include BMPs, IGF-1, IGF-2, TGF-β, fibroblast growth factors (FGFs), and vascular endothelial growth factor (VEGF). Notably, elevated levels of IGF-1 and IGF-2 are typically associated with metabolic disorders often related to DISH, including insulin resistance, dyslipidaemia and obesity. Therefore, the expression of these growth factors could reflect an underlying metabolic dysregulation, and further research will help enhance our understanding of DISH pathophysiology.

Could DISH be a risk factor for vertebral fractures?

Although it may seem counterintuitive, DISH, a hyperostotic disease, may be a risk factor for VFx due to its frequent association with type 2 diabetes, which is a well-known risk factor for fractures; the hypothesised inflammation that can deteriorate cancellous bone; and the abnormal mechanical stress on the vertebral bodies. A recent retrospective study (46) compared 189 patients (137 females) with a recent VFx to 375 age- and sex-matched controls. The impact of DISH on VFx risk varied according to age: in individuals aged 50–59 years, DISH was found to be strongly associated with an increased risk of VFx (adjusted OR for age, sex, and BMD: 7.11); by contrast, DISH had a protective effect against VFx (adjusted OR: 0.495) in patients aged 80 years or more. The severity of ossification and the maximum number

of consecutive ossified segments were significantly associated with VFx risk in the 50–59 years age group, but not in the 60–69 and 70–79 years groups. The increased risk for VFx in younger people may be due to incompletely ossified spinal segments, which generate long lever arms and focal stress concentrations, thereby predisposing to VFx even after low-energy traumas. Conversely, in older adults, the formation of continuous bone bridges and extensive intervertebral ossification may enhance spinal stability and reduce segmental mobility, thereby decreasing VFx risk. The study also highlighted a minor role of BMD in evaluating VFx risk in older patients with DISH, as DXA measurements may overestimate BMD due to ossification. This overestimation can lead to an underestimation of fracture risk, emphasising the need to account for the limitations of DXA in patients with DISH (47).

A recent meta-analysis (48) compared the prevalence of VFx in patients with DISH and in patients of ankylosing spondylitis (AS). Seven studies on DISH and 27 studies on AS published between 1980 and 2023 were included. Despite considerable heterogeneity among the studies, the meta-analysis reported a VFx prevalence of 22.6% and 15.2% in DISH patients and AS patients, respectively. Interestingly, VFx were mostly detected at the thoracolumbar junction (T12-L1) in DISH patients, whereas they were predominantly located in the mid-thoracic spine (T6-T9) in AS patients.

Take home messages

- DISH is a systemic disorder with exuberant ossification at the spine and at peripheral entheses. There is still a lack of consensus on which of several proposed sets of classification criteria is the best to employ (33).
- DISH is closely linked to obesity, metabolic syndrome (40), and CAD severity (42). DISH detection should prompt screening for metabolic and cardiovascular diseases.
- The exact cause of bone formation in DISH is still unclear, but certain growth factors (TGF-β, IGF-, IGF-2, VEGF) and adipokines (*e.g.* leptin,

adiponectin) may play a key role and may serve as target of future therapies (43-45).
- DISH patients seem more prone to developing VFx than healthy controls (46).

Hypophosphatasia

Hypophosphatasia (HPP) is a rare systemic metabolic disorder caused by loss-of-function mutations of the *ALPL* gene, which encodes for the tissue-nonspecific alkaline phosphatase (TNSALP) enzyme. Approximately 500 gene variants, classified as pathogenic, likely pathogenic, or with unknown significance, have been identified (https://alplmutationdatabase.jku.at/table/), and inheritance can be autosomal dominant or recessive. The hallmark of HPP is low serum TNSALP activity (49).

TNSALP is expressed predominantly in bone (osteoblasts and chondrocytes), liver, and kidney. The physiological role of TNSALP is to hydrolyse organic phosphate esters. The three known substrates of TNSALP are inorganic pyrophosphate (PPi), pyridoxal-5´-phosphate (PLP), and phosphoethanalomine (PEA). In HPP, TNSALP loss of function determines PPi accumulation and bone mineralisation impairment, resulting in osteomalacia and/or dental defects. Inefficient dephosphorylation of PLP limits its crossing of the blood-brain barrier, resulting in vitamin B6-responsive seizures in juvenile patients. HPP features several clinical manifestations and a wide range of severity due to both incomplete penetrance and the large array of pathogenic mutations. Signs and symptoms include myalgia, muscle weakness, fatigue, periarticular calcifications, chondrocalcinosis, nephrocalcinosis, nephrolithiasis, and poorly healing fractures, particularly recurrent metatarsal stress fractures or femoral pseudofractures (50, 51). Premature loss of primary or permanent dentition may be the only manifestation, resulting in odontohypophosphatasia (52).

Impairments of physical and psychological functioning and a low health-related quality of life are frequently observed in HPP patients. Moreover,

data from the Global HPP International Registry (NCT02306720) revealed a significant diagnostic delay in HPP, especially in juveniles, leading to a worsening of burden of disease and possibly to damage accrual (50). In Europe, the estimated prevalence of severe HPP is 1:100,000 to 1:300,000 individuals, whereas milder forms may affect 1:6,370 individuals (53).

2024: the year of HPP diagnostic criteria

Until 2023, the lack of diagnostic criteria for HPP has hampered research in this field due to the heterogeneity of patient cohorts across different studies. Recently, the multidisciplinary HPP International Working Group published two articles proposing diagnostic criteria of HPP for adult (54) and juvenile (children and adolescent) patients (55). The authors identified diagnostic biochemical and clinical items of interest for HPP, specifically 17 for adults and 15 for juveniles, and conducted a systematic review and meta-analysis of papers reporting patients with established or suspected HPP and featuring one or more of the items under consideration. Each item was initially classified as major or minor criterion if its pooled prevalence in the literature was >50% or <50%, respectively. The Working Group then discussed the appropriateness of the results and promoted, demoted, or excluded any of the items from the final criteria, according to consensus. Eventually, the authors identified four major and five minor criteria for adults, and four major and nine minor criteria for juveniles (Table II).

In both sets, HPP can be diagnosed if a subject meets two major criteria, or one major and two minor criteria. However, a few concepts should be kept in mind. The presence of low (for age and sex) serum levels of TNSALP activity was regarded as an obligate criterion, provided that it has been observed in at least two measurements separated by enough time and alternative causes of hypophosphatasaemia have been excluded. Caution should be paid to certain conditions, such as pregnancy or recent long bone fractures, which may temporarily normalise TNSALP meas-

Table II. Diagnostic criteria for HPP in adults and juveniles.

Adults (54)	
Obligate criterion: Low TNSALP enzymatic activity for age and sex	
Major criteria	**Minor criteria**
Pathogenic or likely pathogenic *ALPL* gene variant(s)	Poorly healing fractures
Elevation of natural substrates of TNSALP	Chronic musculoskeletal pain
Atypical femur fractures	Early atraumatic loss of teeth
Recurrent metatarsal stress fractures	Chondrocalcinosis
	Nephrocalcinosis

Juveniles (55)	
Obligate criterion: Low TNSALP enzymatic activity for age and sex	
Major criteria	**Minor criteria**
Pathogenic or likely pathogenic *ALPL* gene variant(s)	Short stature
Elevation of natural substrates of TNSALP	Delayed motor milestones
Early non-traumatic loss of primary teeth	Chronic musculoskeletal pain
Presence of rickets on radiograph	Impaired mobility
	Genu valgum/varum
	Craniosynostosis
	Nephrocalcinosis/nephrolithiasis
	Low muscle tone
	B6-responsive seizures

Note: the patient's current age, and not the patient's estimated age at HPP onset, must be considered to guide the choice of the set of criteria to be employed.

urements in individuals who could be actually affected by HPP. Lastly, for patients presenting with a pathogenic *ALPL* mutation and low TNSALP levels in the absence of clinical criteria, the Working Group deemed necessary that PLP, PEA, and PPi be assessed before excluding HPP.

Although family history of HPP is important in medical history taking, it was not deemed a valid diagnostic criterion because it may lead to HPP diagnosis even in asymptomatic individuals with only molecular or biochemical findings, in the absence of clinical manifestations. Decreased BMD and/or osteoporosis were excluded from the criteria. The authors discouraged the use of DXA in HPP patients, where BMD is frequently not reduced even in severe cases; moreover, DXA cannot detect osteomalacia, which is the actual bone involvement observed in HPP. Osteomalacia was not included either because bone histomorphometry is rarely available in routine clinical practice (55).

In conclusion, the two recently proposed diagnostic criteria represent a milestone as they finally provide a guide to detect HPP, whose diagnosis has been traditionally challenging due to unawareness, its numerous unspecific signs and symptoms, and broad

differential diagnosis. Since fragility fractures may occur in HPP patients, it is of outmost importance that the bone specialist be able to recognise HPP to avoid a misdiagnosis of osteoporosis and a harmful treatment with bisphosphonates, which are contraindicated in HPP due to the high risk of atypical femoral fractures resulting from a further decreased bone turnover. Furthermore, researchers can now benefit from a useful tool to uniform HPP cohorts.

Enzyme replacement therapy (ERT) in HPP

Asfotase alfa, a human recombinant TNSALP, was the first ERT for patients affected by perinatal/infantile and juvenile-onset HPP to be approved in the United States and in Europe.

Kishnani *et al.* (56) recently analysed data from the Global HPP Registry to assess the real-world effectiveness of asfotase alfa in 190 adult HPP patients who were treated for at least 6 months. The authors evaluated mobility using the 6-minute walking test (6MWT) and pain and disability using patient-reported outcomes at several timepoints over a period of 36 months. At the end of follow-up, the mean distance walked during the 6MWT at 36 months significantly increased from baseline by a mean of

45 meters, with statistical significance reached already at 12 months, where the increase was most pronounced by a mean of 93 meters. At all timepoints, a significant improvement was also observed in terms of pain severity score, pain interference score, and worst pain in the past 24 hours. Disability scores did not change, but the number of patients without disability increased from baseline (18.3% *vs*. 8.6%). Injection site reactions were observed in 12% of patients, and serious adverse events occurred in 7 patients.

Efzimfotase alfa (ALXN1850), a second-generation ERT, is structurally similar to asfotase alfa but has several modifications which enhanced drug affinity to bone and improved pharmacokinetics. A recent phase I study on 15 adults with a clinical diagnosis of HPP proved that efzimfotase alfa had safety and tolerability profiles comparable to those seen with asfotase alfa but showed higher dose-normalised systemic exposure (57). Therefore, efzimfotase alfa may have similar efficacy along with the advantage of lower doses, smaller injection volumes, and less frequent administrations compared to asfotase alfa, thus potentially reducing injection site reactions and improving quality of care and patient compliance. Furthermore, it reduced plasma levels of PPi, suggesting that it could improve bone mineralisation. Ongoing phase III studies of efzimfotase alfa (NCT06079359, NCT06079281, and NCT06079372) are evaluating its safety and efficacy *versus* placebo on functional outcomes (6MWT, Sit-To-Stand test, and Time Up and Go test) in HPP patients who have not never been treated with asfotase alfa.

Take home messages
- HPP is a rare but potentially disabling disease. The prevalence of milder forms may be higher than previously estimated. Diagnostic delay contributes to disease burden (50).
- Diagnostic criteria for HPP are finally available (54, 55). Their use in both clinical and research settings will likely contribute to a better understanding of the disease and will help reduce diagnostic delay, cases of misdiagnosis, and medication errors.
- ERT with asfotase alfa is available for perinatal/infantile and juvenile-onset adult HPP patients (56). Efzimfotase alfa, a second-generation ERT, showed promising results (57) and is currently being investigated in phase III studies involving both juveniles and adults.

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