Rheumatology Advances in Practice, 2024, **8(2)**, rkae061
https://doi.org/10.1093/rap/rkae061
Advance access publication 24 May 2024
Systematic Review and Meta-Analysis

British Society for Rheumatology
RHEUMATOLOGY ADVANCES IN PRACTICE
OXFORD

Clinical science

Disease-specific definitions of new bone formation on spine radiographs: a systematic literature review

Ummugulsum Gazel[1,*], Gizem Ayan [1], Nicole Hryciw[2], Jean-Philippe Delorme[3], Elliot Hepworth[1], Marcos Sampaio[3,4], Zaid Jibri[3,4], Jacob Karsh[1,5], Sibel Zehra Aydin[1,5]

[1]Division of Rheumatology, Department of Medicine, The Ottawa Hospital, Ottawa, ON, Canada
[2]Department of Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada
[3]Department of Radiology, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada
[4]Division of Radiology, Department of Medical Imaging, The Ottawa Hospital, Ottawa, ON, Canada
[5]Ottawa Hospital Research Institute, Ottawa, ON, Canada

*Correspondence to: Ummugulsum Gazel, Rheumatology Department, University of Ottawa, 1967 Riverside Dr, Ottawa, ON K1H 7W9, Canada.
E-mail: gulsumoguz@hotmail.com

Abstract

Objectives: We aimed to explore the radiographic definitions of types of New Bone formation (NBF) by focusing on the terminology, description and location of the findings.

Methods: Three systematic literature reviews were conducted in parallel to identify the radiographic spinal NBF definitions for spondyloarthritis (SpA), Diffuse Idiopathic Skeletal Hyperostosis (DISH) and Osteorathritis (OA). Study characteristics and definitions were extracted independently by two reviewers. Definitions were analysed and collated based on whether they were unique, modified or established from previous research.

Results: We identified 33 studies that indicated a definition for the NBF in SpA, 10 for DISH and 7 for spinal OA. In SpA, the variations in syndesmophytes included the description as well as the subtypes and locations. The differentiation of syndesmophytes from osteophytes were included in 12 articles, based on the origin and the angle of the NBF and associated findings. The definitions of DISH varied in the number of vertebrae, level and laterality. For OA, five articles indicated that osteophytes arose from the anterior or lateral aspects of the vertebral bodies, and two studies required a size cut-off.

Discussion: Our ultimate aim is to create formal NBF definitions for SpA, DISH and OA guided by an atlas, through a Delphi exercise with international experts. The improved ability to differentiate these conditions radiographically will not only allow the clinicians to accurately approach patients but also will help the researchers to better classify patient phenotypes and focus on accurate radiographic outcomes.

Lay Summary

What does this mean for patients?
Bone spurs are bony growths that form along the edges of bones. Bone spurs can occur in the spine in different diseases, such as spondyloarthritis, osteoarthritis and diffuse idiopathic skeletal hyperostosis, which may look very similar when using medical imaging techniques. It is not clear why diseases with different mechanisms result with similar bone spurs. Distinguishing these bone spurs can be challenging, especially in older people. In this study, we reviewed existing studies to see how these bone spurs are defined on spine radiographs (a type of X-ray) in different diseases. We found that the definitions vary greatly based on the bone spurs' forms, shape, size and level on the spine. Using this information, we aim to ultimately standardize the descriptions of bone spurs from each other depending on the underlying disease.

Keywords: new bone formation, spine, radiography.

Key messages

- New bone formation can be seen in spondyloarthritis, osteoarthritis and DISH, with different underlying pathogenic mechanisms.
- Literature shows the heterogeneity in the definition of new bone formation on spine radiographs.
- The terminology of new bone formation in different diseases needs to be established.

Introduction

New bone formation (NBF) and destruction cycles provide normal bone turnover in a balanced and continuous manner. Osteoblasts play the main role in synthesis of new bone to maintain bone homeostasis. NBF occurs as a result of tissue repair mechanisms mediated by inflammatory, non-inflammatory and biomechanical forces [1].

Despite increasing research in this area, the cellular and molecular processes of NBF in humans are poorly understood. Bone morphogenic protein and wingless-type-like signalling

Received: 7 September 2023. **Accepted:** 24 March 2024

pathways found to have a critical role in NBF in animal studies in spondyloarthritis (SpA) [2]. Furthermore, the complex bone remodelling mechanism of osteoblastic NBF with the interaction of cellular proliferation, differentiation, maturation, migration and cell death has been described in SpA. However, these osteoblastic changes are not specific to SpA, and a similar remodelling process can be seen in the degenerative changes in the spine leading to spinal damage Osteorathritis (OA) and Diffuse Idiopathic Skeletal Hyperostosis (DISH) [3, 4].

Regardless of the underlying mechanism, processes of NBF can sometimes occur in the same patient [5, 6]. Therefore, it can be challenging to differentiate NBFs in SpA, OA and DISH by conventional radiography. Moreover, these conditions can frequently coexist, which has been demonstrated to be related to a poorer outcome, and the management can be challenging [5, 7]. For example, marginal syndesmophytes can be mistaken for the early osteophytes, and bridging osteophytes mimic bridging para-marginal syndesmophytes [8, 9]. The ability to distinguish these entities through radiographic imaging holds clinical significance due to the diverse prognoses and differences in the treatment approaches associated with each. Differentiating the aetiology of NBF is also very important for the research on the pathogenesis of these diseases. This may be problematic in clinical trials that use radiographic progression on the spine as an outcome and has the potential to result in high rate of measurement error.

We believe an important element in establishing a comprehensive definition of radiographic spinal NBF is to review the radiographic definitions that are currently utilized in the literature. Our ultimate aim is to have a consensus on the definitions of NBF in order to differentiate NBF types from each other. We conducted three parallel systematic literature reviews (SLR), aiming to explore the definitions of various types of NBF in DISH, OA and SpA and combined results in this article. We will use the results to inform an international Delphi through an atlas to establish criteria to identify and differentiate NBF in each of these disease processes, which will be followed by prospective research to validate our efforts.

Methods

Study selection and search strategy

Three separate SLRs were performed by using a predefined PICO (population, intervention, comparator and outcome) strategy. MEDLINE, EMBASE and Cochrane Central Register databases were reviewed for publications between January 1980 and November 2023 by an experienced librarian (RS) at The University of Ottawa. Our research questions were identified as follows: 'What are spine NBF radiography findings in patients with 1) DISH, 2) spine OA, 3) PsA, 4) AS, 5) SpA?'

Search strategies have been developed separately for these research questions. The following terms have been used for the literature search; 'PsA' OR 'AS' OR 'Spondyloarthritis' OR 'Spine osteoarthritis' OR 'DISH' AND 'Radiography' AND 'Spine' as MESH terms and text terms. Review process was done after merging the results of three diseases under the SpA topic.

The protocols have been registered to the International Prospective Register of Systematic Reviews database (Registration numbers for DISH: CRD42020197545, for OA: CRD42020197584, for SpA: CRD42020197760). Details of search strategies are given in Supplementary Tables S1–S3, available at *Rheumatology Advances in Practice* online.

The titles and abstracts were independently screened by two reviewers (UGG&GA for SpA, NH&JD for DISH and OA). All abstracts with discrepancies were carried forward to a full-text review, to be as inclusive as possible, and the full texts were reviewed independently by the same investigators. Any disagreement at the stage of full text review was resolved by the third investigator (SZA). Articles that do not fulfil the inclusion criteria were identified, and the reason for exclusion was documented. Additionally, references of the included articles were manually searched. All screening processes for three SLRs were presented in a flow chart (Fig. 1). To be eligible for inclusion, studies had to meet the following criteria; either cross-sectional, case–control, cohort, observational (retrospective or prospective) study designs, literature reviews and case studies with more than 10 patients; studies including patients >18 years old with a diagnosis of SpA (AS, PsA, inflammatory bowel disease-associated arthritis, reactive arthritis), DISH or OA with the descriptions of axial plain radiographic NBF features and utilized this definition for diagnosis. Studies were excluded if they were in a language other than English, the wrong study type, with no displayed or inaccessible data, duplicate study population, the wrong outcome or modality (e.g. computed tomography or magnetic resonance imaging) or if only the abstract was available.

Data extraction

After identifying of the articles to be included, data were extracted in parallel by two independent reviewers using a standardized sheet (UGG&GA for SpA, NH&JD for DISH and OA). Any discrepancies within the data extraction phase were resolved by discussion with a third reviewer (SZA). The descriptions of axial plain radiographic NBF features in patients with DISH, OA and DISH were the primary outcomes.

The location (cervical/thoracic/lumbar) and distribution of age groups of the defining disease types were the secondary outcome measures.

Results

The results of the SLRs are presented separately for SpA, DISH and OA:

SpA

Our literature search identified 32 studies (11 original studies and 21 review articles), which included a definition of NBFs on the spine radiography of SpA patients. The diagnostic subgroups, sample size, age distribution and spinal region in the original studies, as well as the definitions, were displayed in Table 1. For the review articles, definitions and disease subgroups were summarized in Supplementary Table S4, available at *Rheumatology Advances in Practice* online.

Definition of syndesmophytes

Our literature search was able to identify only one description of syndesmophytes, that was used in 13 studies with only minor modifications [10–22]. According to that, a syndesmophyte was defined as 'bony overgrowth (protuberances/projections) along the anterior longitudinal ligament or ossification within the outer fibres/layers of the annulus

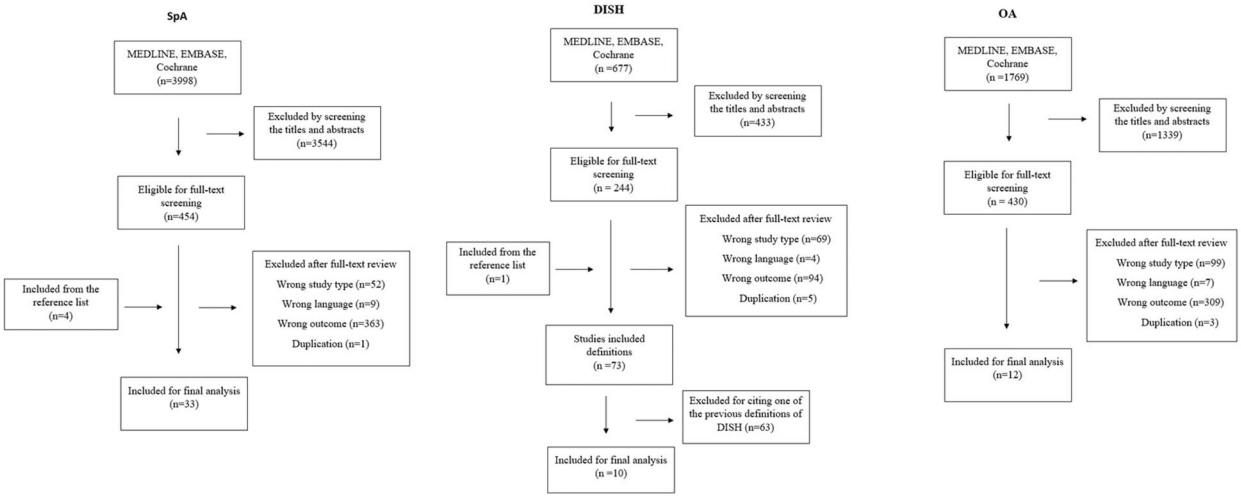

Figure 1. Flow chart for study selection

fibrosus'. In the majority of these articles, syndesmophytes' shape was specified as thin and the orientation of the growth as vertical. Six of the 12 articles mentioned that syndesmophytes may also connect the angles of adjacent vertebral bodies or connect two vertebral bodies across the disc space, leading to bridging phenomena, although this was not a mandatory feature of the definition [12–15, 19, 21].

Definition of subtypes of syndesmophytes

Marginal syndesmophytes: Seven articles used a specific terminology of 'marginal syndesmophytes' [14, 23–28]. Six of these articles defined the marginal syndesmophytes as 'vertebral ossifications/calcification/bony outgrowth arose from the edge of the vertebral body vertically and extend from the corner of one vertebra to the next'. Mattar *et al.* [14] defined the marginal syndesmophytes as 'horizontal projections at the level of the vertebral end-plate, with its cortex and medulla continuous with those of the parent bone'. Also, three of seven articles additionally described them as 'being thin' [23, 27, 28].

Non-marginal (para-marginal) syndesmophytes: Within the included studies, eight articles had a definition for non-marginal (para-marginal) syndesmophytes [23, 26–32]. Three out of eight articles described the growing pattern of these NBFs as syndesmophytes arising from beyond/away from the edge/margin of the vertebral body [23, 26, 31]. Five articles stated that these bony growths are curvilinear. Also, the following features for the shape of para-marginal syndesmophytes were mentioned in the articles: asymmetrical, thick, bulky, fluffy and chunky. While three articles described these ossifications as being parallel to the vertebral bodies or intervertebral discs [29, 31, 32], Eshed *et al.* [27] defined them as horizontally oriented syndesmophytes.

Other NBF definitions in SpA

Paravertebral ossification: Four articles included the definition of paravertebral ossification. These ossifications were defined as being close to the vertebra; however, with a gap between the margins of the ossification and the vertebra [23, 28]. Also, Klecker *et al.* [31] described it as 'coarse asymmetrical bony bridging, and relative sparing of the apophyseal joints'.

Squaring: Squaring of vertebral borders was described as a result of erosive changes at the corners of the vertebrae and straightening of the anterior curve of the vertebra by NBF. This lesion is defined as a typical feature of AS and is best visualized in the lumbar spine [12, 33, 34].

Finer ossification: It was separately defined only by Porter *et al.* as 'more closely related to the disc margins and fusing with the rim of the vertebral body'.

Locations of the NBF in SpA

Among 11 original articles, five investigated the syndesmophytes on the cervical and lumbar spine, while six articles included the thoracic spine as well (Table 1). For para-syndesmophytes, three articles specifically indicated that the lower thoracic and upper lumbar spine or thoracolumbar junction were more commonly involved than the cervical and lower lumber spine [31, 32]. However, Sudol-Szopinska *et al.* [29] mentioned that cervical involvement may be typical for the para-marginal syndesmophytes in PsA.

For the other lesions, in two articles, squaring of vertebra was mentioned as they can be best visualized in the lumbar spine due to the concavity of the lumbar spine compared with the cervical and thoracic spine [33, 34].

Differentiation of the inflammatory lesions from degenerative changes

A differentiation between syndesmophytes and degenerative changes was made in 12 articles [5, 12, 13, 18, 21, 26, 35–40]. According to those articles, syndesmophytes originated at the ligamentous insertion and the growth was parallel to the anterior vertebral side/anterior intervertebral ligament, whereas osteophytes originated from the cartilaginous end-plate, with a horizontal growth and was associated with disc space narrowing.

In parallel to this explanation, in five articles, an angle of 45° was used to differentiate, with SpA-related changes having an angle of ≤45° to the anterior vertebral side and an angle of > 45° being representative of degenerative changes [5, 12, 37, 38, 40].

Distinguishing spinal PsA findings from other SpA subtypes

Non-marginal syndesmophytes were indicated to be more typical for PsA [27, 29]. The main differences for NBF in PsA

Table 1. Original studies with NBF definitions in SpA

Author/year	Country	SPA Type	Diagnosis criteria used	Study design	Sample size (*n*)	Gender (M/F)	Age	Anatomical site	Definition
Petcharat *et al.* (2021) [22]	Thailand	AS and PsA	AS: Modified New York criteria PsA: Caspar Criteria	Cross-Sectional	AS: 153 PsA :166	171/148	45.5 (12.2)	Cervical and lumbar spine	'Syndesmophyte was defined as bone growth originating from the vertebral endplate in the anterior one-quarter of the discovertebral space or from the anterior vertebral cortex'
Gonzalez-Lopez *et al.* (2017) [10]	Mexico	AS	New York criteria	Prospective/ case–control	89	57/32	44.3 (11.4)[a]	Cervical/ Lumbar	'Syndesmophytes were defined as bony protuberances associated with ossification of the spinal ligaments without involvement of the intervertebral discs'.
De Bruin *et al.* (2016) [35]	Netherlands	AxSpA	ASAS	Cross-sectional	274	96/178	28.2 (9)[a]	All	'The differentiation between osteophytes and syndesmophytes is based on the site of origin and the angle between the bony spur and the vertebral endplate; syndesmophytes originate at the ligamentous insertion and have a more vertical configuration'.
Gamez-Nava *et al.* (2016) [11]	Mexico	AS	New York criteria	Case–control	78	50/28	Male: 45 (26–63)[b] Female: 48 (23–64)[b]	Cervical/ Lumbar	'Syndesmophytes were defined according to the presence of ossification of vertebral ligaments of $>$ 5 mm in radiographs'.
Baraliakos *et al.* (2014) [36]	Germany	AS	N/A	Cross-sectional	73	63/10	40.5 (10.5)[a]	Cervical/ Lumbar	'Assessment of syndesmophytes and differentiation from degenerative changes such as spondylophytes was made according to a recent proposal, where the former are considered by showing a growth parallel to the anterior vertebral side/anterior intervertebral ligament while the latter are considered by showing a growth parallel to the horizontal line'.
Haddad *et al.* (2013) [5]	Canada	PsA	CasparS	Prospective cohort	78	57/21	62.9 (8.9)[a]	Cervical/ Lumbar	'PsA-related changes (syndesmophytes) were considered if there was a growth angle of $<$ 45° to the anterior vertebral side, while an angle $>$ 45 was considered to be osteophytes'.
Baraliakos 2012 [37]	Germany	AS	mNew York criteria	Retrospective cohort	146	81/65	54.2 (12.3)[a]	Cervical/ Lumbar	'Measuring the horizontal angle of new bone formation on lateral spinal radiographs, AS-related changes (syndesmophytes) were assumed to typically show a growth angle of $\leq$ 45° to the anterior vertebral side, while a growth angle of $>$ 45° was assumed to represent more DISH-related changes (spondylophytes)'.
Maejima *et al.* (2010) [23]	Japan	PsA	Caspar	Cross-sectional	25	18/7	N/A	All	'Marginal syndesmophyte is classic and a thin syndesmophyte arises vertically from the annular attachment to the vertebral body. Non-marginal syndesmophyte is a vertically oriented or curvilinear syndesmophyte, often thick and chunky, arising from beyond the annular attachment to the vertebral body. Paravertebral ossification is ossification close to the vertebral body, but with a clearly defined gap between the margins of the ossification and the vertebral body'.
Chandran *et al.* (2009) [24]	Canada	PsA	N/A	Retrospective cohort	297	169/128	42.5[a]	All	'Marginal syndesmophytes were recorded if the vertebral ossifications arose from the edge of the vertebral body and formed a fine vertical bridge, and paramarginal syndesmophytes were described when the ossification arose away from the edge of the vertebra and was board and coarse.

(continued)

Table 1. (continued)

Author/year	Country	SPA Type	Diagnosis criteria used	Study design	Sample size (*n*)	Gender (M/F)	Age	Anatomical site	Definition
									Syndesmophytes were distinguished from osteophytes in that the latter, which originate from the cartilaginous endplate in response to degeneration of the disc, are wider, horizontally oriented and are associated with narrowed disc spaces'.
Baraliakos 2007 [38]	Germany	AS	mNew York criteria	Prospective	116	N/A	38.4[a]	All	'Bony changes with an angle ≤45° to the anterior vertebral side were defined as syndesmophytes, in contrast with changes with an angle of >45°, which were defined as ambiguous syndesmophytes'.
Helliwell *et al.* (1998) [25]	UK	AS/ PsA/ IBD/ Reactive arthritis	AS = New York criteria ReA = Calin criteria		AS = 91, IBD = 31 ReA = 5 PsA = PsA		AS: 46[a] IBD = 48 PsA = 46 ReA = 43	All	'Paravertebral ossification as defined and described by Bywaters and Dixon, ligamentous calcification (usually interspinous ligament), squaring of the anterior border of the vertebra without erosion/sclerosis, discitis (narrowing of disc space with erosion and new bone formation in adjacent vertebrae), spinal pseudarthrosis (a fracture line through a fused spine with reactive new bone formation at either side of the lesion), bamboo spine (complete ankylosis of vertebrae due to contiguous syndesmophyte formation) and ankylosis of zygoapophyseal joints. Syndesmophytes were classified as chunky or marginal based on their size and shape. Marginal syndesmophytes were defined as discrete vertically oriented areas of calcification extending from the corner of one vertebra to the next. Chunky syndesmophytes were defined as more extensive areas of calcification extending vertically from the vertebral corner included within this group were the non-marginal and 'inverted comma' syndesmophytes of McEwen *et al.*'
Hanly *et al.* (1988) [26]	Canada	PsA	NA	Cross-sectional	52	30/22	44 (23–70)[b]	All	'Marginal syndesmophytes were recorded if the vertebral ossifications arose from the edge of the vertebral body and formed a fine vertical bridge and paramarginal syndesmophytes were described when the ossification arose away from the edge of the vertebra and was broad and coarse. Syndesmophytes were distinguished from osteophytes in that the latter, which originate from the cartilaginous end plate in response to degeneration of the disc, are wider, horizontally oriented and are associated with narrowed disc spaces. Paramarginal syndesmophytes were also distinguished from diffuse idiopathic skeletal hyperostosis (DISH) in that the latter condition occurs in four or more consecutive vertebrae, involves primarily the right side of the thoracic spine and is associated with normal sacroiliac joints'.

[a] Mean (S.D.).
[b] Median.
SpA: Spondyloarthritis; AxSpA: Axial Spondyloarthritis; ASAS: Assessment of Spondylo Arthritis International Society; ReA: Reactive arthritis; N/A: Not applicable.

Table 2. Dichotomous criteria for the radiographic diagnosis of spinal DISH

Original Author	Description
Haddad *et al.* 2013 [5]	'… flowing bony bridges on the right aspect of at least four contiguous thoracic vertebrae seen on anteroposterior view and also confirmed to be flowing on the lateral thoracic spine radiograph, irrespective of the presence of radiographic sacroiliitis on the last available radiographic assessment'.
Denko *et al.* 2002 [47]	'Patients with DISH met the following criteria … All DISH patients were 45 years or older with symptoms of pain in the spine and characteristic radiological changes in the involved areas consisting of widened intervertebral disk space and exuberant osteophytosis'
Guo *et al.* 1997 [46]	'… flowing ossification of at least four contiguous vertebral bodies'
Marcelli *et al.* 1995 [45]	'(1) Presence of flowing calcification and ossification along the anterolateral aspects of at least three contiguous vertebral bodies; (2) Presence of two (or more) flame-shaped anterolateral bony bridges over the intervertebral disc spaces in the same segment of the spine (3) Clear predominance of the lesions on the lower thoracic and upper lumbar region (although both sides of the vertebral column are frequently involved)'
Rogers *et al.* 1987 [48]	'… the presence of massive vertical osteophytes on the right anterolateral surface of the bodies of the thoracic spine … The vertebrae may be ankylosed but disc spaces are normal and the facet joints … are almost always normal … there must also be extraspinal manifestations of new bone growth in ligaments, in tendinous insertions or in cartilage'.
Arlet and Mazières, 1985 [41]	'(1) Bridging ossification of three adjoining vertebrae in the thoracic region. (2) Absence or minimal intervening disc disease. (3) No facet joint ankylosis. (4) Absence of sacroiliac joints erosion or ossification'
Brigode *et al.* 1982 [42]	To be included in the vertebral ankylosing hyperostosis series, patient had to have 'at least two complete intervertebral bridges and a typical bone case along one vertebral body'
Resnick and Niwayama, 1976 [4]	'(1) Flowing ossifications and/or calcifications along the anterolateral aspect of at least four contiguous vertebral bodies, with or without osteophytes; (2) Preservation of intervertebral disc height in the affected areas (to differentiate from degenerative disc disease) (3) Absence of bony ankylosis of facet joints, sacroiliac erosion, sclerosis or fusion (to differentiate from ankylosing spondylitis)'
Julkunen *et al.* 1975 [44]	'… prominent and complete bony bridge connecting two vertebrae in two or more different sites in the dorsal spine'
Forestier and Lagier, 1971 [43]	'(1) Flowing calcification at the anterolateral aspect of three vertebral bodies in the dorsal spine, thus forming two intervertebral 'bridges'; (2) 'Relative' preservation of disc height in the vertebral region involved; (3) Absence of sacroiliac lesions such as erosion, sclerosis and bony ankylosis, as well as absence of ankylosis in the posterior apophyseal joints (all these being present in ankylosing spondylitis, which is an inflammatory enthesopathy)'

DISH: Diffuse idiopathic skeletal hyperostosis.

compared with other SpA entities were larger, asymmetric distribution with skipped vertebral bodies levels, unilaterality and separation from the lateral aspect of the vertebral bodies of syndesmophytes [27, 29, 40]. Also, in Reijnierse *et al.*'s [12] study, ossification in AS was specified as in the outer layers of the annulus fibrosus itself, which results as intervertebral bridging, while PsA-related ossification was indicated as paraspinal and separated from the vertebral bodies and discs.

DISH

Our literature search identified several dichotomous variations in the radiographic definition of spinal DISH, that could be grouped into 10 definitions in total (Table 2).

Definitions of DISH

Number of vertebrae: Within the 10 dichotomous definitions outlined, five definitions [41–45] required the involvement of at least three contiguous vertebrae (or two intervertebral bridges), and three definitions [4, 5, 46] required four contiguous vertebrae to classify as changes as consistent with DISH. Two studies [47, 48] did not require any specific number of contiguous vertebrae as part of their definition of DISH.

Level of NBF: Five out of 10 definitions [5, 41, 43, 44, 48] mandated that lesions of NBF consistent with DISH were found on the thoracic spine, and one definition [45] required the presence of changes in the thoracic or lumbar spine. None of the definitions specified criteria for cervical spine changes. There were four definitions [4, 42, 46, 47] that did not specify a spinal level of involvement to make the diagnosis of DISH.

Laterality: Two out of 10 definitions required the ossifications to be present on the right side [5, 48].

Description of NBF in DISH

Several descriptions of the bony lesions of DISH were found in the identified dichotomous definitions. The most common description specified changes as flowing or bridging ossifications/calcifications, found in seven of the definitions [4, 5, 37, 41, 43, 46]. Other descriptions included were exuberant osteophytosis [47], flame-shaped anterolateral bony bridges [45] and massive vertical osteophytes [48], all used in one definition each.

Differentiation of the DISH NBF from osteophytes

Most of the definitions differentiated DISH-related changes from OA by requiring a normal/relatively normal disc space.

Preservation of disc height was mandated in five definitions [4, 41, 43, 47, 48], one of which specifically included 'widening intervertebral disc space' [47]. None of the studies included differentiation of NBFs of DISH and OA. One study described the NBF in DISH as osteophytes.

Differentiation of the DISH NBF from syndesmophytes

Three definitions [4, 41, 43] required the absence of sacroiliitis in order to make a definitive diagnosis of DISH [49, 50], with each of these definitions also including the absence of ankylosis in the facet joint and one in the apophyseal joint [43]. Outside of the 10 dichotomous definitions identified by our search, one study modified the classically accepted Resnick criteria to help differentiate the NBF of DISH and SpA based on the angle of new bone growth from the vertebrae, which was then used in another study [7, 37]. In both studies, a growth angle of $>45^\circ$ from a vertebral body was felt to be in keeping with DISH-related changes, whereas bony growth of $\leq 45^\circ$ was felt to be in keeping inflammatory changes, either from PsA [7] or AS [37].

OA

There were seven studies identified that provided a definition for the identification of osteophytes in the context of spinal OA (Table 3).

Radiographic definitions for spinal osteophytes

Location of NBF: A total of five articles indicated that osteophytes arose from the anterior or lateral aspects of the vertebral bodies, with only two of these studies specifying that osteophytosis could also occur at other locations, including the posterior, superior and inferior margins [51, 52].

Size of NBF: Two studies required a size cut-off in their definitions of osteophytes in the context of OA. Pfirrmann *et al.* [53] classified large osteophytes as those with an 'anteroposterior diameter greater than 3 mm'. Another study required the presence of osteophytes longer than 2 mm to define spondylosis [54].

Description of NBF: Of the seven studies that included definitions for osteophytes, five described osteophytes as a form of outgrowth or spur arising from the bone [51, 52, 54, 55]. One study simply defined osteophyte as 'prominent bony proliferation' [53].

Osteophyte subtypes: Two articles defined different subtypes of osteophytes [53, 55]. Both studies outlined criteria for traction osteophytes, and one of the articles also defined claw osteophytes. These definitions were based on the shape and direction of growth of the osteophyte itself. Traction osteophytes were noted to grow horizontally in both aforementioned studies.

Radiographic definitions for spondylosis

Eight studies were identified that outlined specific criteria for the diagnosis of spondylosis (Supplementary Table S5, available at *Rheumatology Advances in Practice* online). All studies defining spondylosis included the presence of osteophytes in their criteria for diagnosing spondylosis. Osteophytes were often an absolute criterion for the diagnosis of spondylosis, but not in every case. In all but one study, disc space narrowing was also included in the criteria for the definition of spondylosis, though it was not necessary to make the diagnosis in any study. Three articles included facet joint sclerosis in their descriptions of spondylosis.

Discussion

Our results showed heterogeneity and variations in defining NBF in these three diseases. For SpA, our SLR revealed the inconsistencies in the literature for the definitions of syndesmophytes in terms of the shape, location and growing patterns of syndesmophyte subtypes. Also, this study identified that there are many variations of definitions of spinal DISH in the literature, which may result in different outcomes. Osteophyte formation was the only feature consistently included in the definition of spinal OA. Otherwise, joint space narrowing was frequently part of the diagnostic criteria, but the inclusion of other features was variable. These results are important to generate knowledge on how the NBFs are defined in the literature and create a standardized approach in this field.

The pathophysiological mechanism of the NBF leading to ankylosis in SpA is still unclear. The slow progression of the process requires a long-term follow-up, making it difficult to understand the natural course. In addition, the spine is not accessible for the purpose of the biopsies. Previously, it has been suggested that inflammation is the initial lesion, followed by the replacement of the subchondral bone marrow by fibrosis as a repair mechanism [56]. On the other hand, it has also been shown that syndesmophytes can grow from the areas without inflammation [36, 57]. According to this hypothesis, there might be similar underlying mechanisms in inflammatory and degenerative diseases, such as mechanical and genetic factors. For example, in DISH, where the metabolic conditions have been identified as the underlying factors, the extra spinal NBF can be seen in similar locations as SpA, such as ligaments, tendons and entheses. Therefore, it may become even more complicated to differentiate SpA from DISH [58–60]. On the other hand, DISH and SpA can also occur concomitantly, with some observation that this co-occurrence may portend worse clinical outcomes [7]. A small study comparing patients with DISH and AS demonstrated that there was a preponderance of horizontal enthesophytes in the former versus vertical enthesophytes in AS [61]. In two studies, authors attempting to differentiate spinal DISH from inflammatory arthritis used the angle of new bone growth in the spine to differentiate these two processes [7, 37]. To our knowledge, this is the only attempt in the literature on plain radiographs to differentiate the two types of NBF based on the angle, which is based on the expert opinion and has not been validated. Research on the bony changes of DISH utilizing computed tomography scans has also suggested an osteophyte angle of larger than 90° in relation to the vertebral bodies to differentiate DISH from bridging degenerative osteophytes, which has not been defined or tested in plain radiographs [62]. It will be important for any future definitions of DISH to take concurrent cases of seronegative spondyloarthropathies and DISH into consideration rather than excluding inflammatory arthritis entirely as is traditional.

From a diagnostic perspective, a clear and comprehensive definition of OA will enable clinicians to differentiate other concurrent skeletal disease processes of NBF. Overlapping features of OA and inflammatory arthropathies have also been reported [63]. For instance, enthesophytes, more classically connected to inflammatory processes, have been associated with OA in patients where SpA has been excluded [63, 64]. Erosive OA, an uncommon presentation of OA, can be especially difficult to discern from other inflammatory

Table 3. Definitions of osteophytes identified in the literature

Author (year)	Country	Study design	Age (mean)	Sample size (*n*)	Anatomical site	Definition
Okpala (2018) [52]	Nigeria	Retrospective	44.7	581 (329 cases, 252 controls)	Lumbar	'… bony overgrowths especially at the anterior, lateral and less commonly, posterior aspects of the superior and inferior margins of vertebral bodies'
Middleto and Fish (2009) [51]	USA	Review	N/A	N/A	Lumbar	'… bony outgrowths arising primarily along the anterior and lateral perimeters of the vertebral end-plate apophyses. These hypertrophic changes are believed to develop at sites of stress to the annular ligament and most commonly occur at thoracic T9–10 and lumbar L3 levels, vacuum phenomenon and vertebral body reactive change'.
Gallucci *et al.* (2007) [55]	Italy	Review	N/A	N/A	Cervical, Thoracic, Lumbar	'Osteophytes are bony spurs that originate on the anterolateral aspect of the vertebral bodies a few millimetres from the margins of the disc space. Posterior osteophytes more frequently accompany osteophytes associated with osteochondrosis, microinstability and disc degeneration. They are characterized by a bulky triangular shape and have a marginal location'
Pitkanen *et al.* (2002) [54]	Finland	Retrospective	43	215	Lumbar	'Traction spur defined as horizontally directed and arising at the site of attachment of the outermost annular fibres about 2 mm away from the distal border of the anterior and lateral surfaces'
Jaovisidha *et al.* (2000) [66]	Thailand	Retrospective	58.8	100	Lumbar	'Osteophyte defined as a prominent bone proliferation along the anterior and lateral aspect of vertebral body.
Pfirrmann and Resnick (2001) [53]	USA	Retrospective	68.2	100	Thoracic, Lumbar	Large osteophytes were defined as outgrowths with an anteroposterior diameter was greater than 3 mm'. 'Claw-type osteophytes were defined as excrescences arising from the discovertebral junction that were triangular and curved at their tip; traction osteophytes were defined as linear osseous plates extending in a horizontal direction throughout their length'.
Katevuo *et al.* (1985) [67]	Finland	Prospective	46.2	311	Cervical, Thoracic	'Spondylosis was recorded if there were changes in more than two vertebrae and if there was osteophytes longer than 2 mm'.

N/A: Not applicable; USA: United States of America.

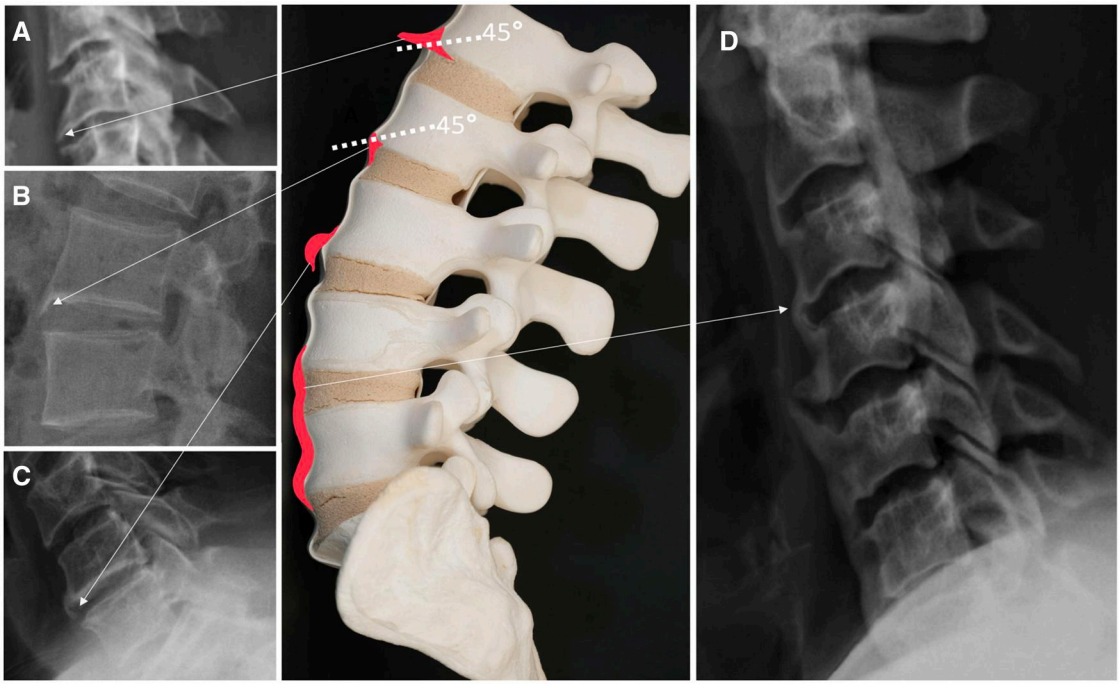

Figure 2. Illustration of some of the new bone formation (NBF) types and representative radiographs. (A) Osteophyte: Horizontal bony outgrowth, with an angle of $>45°$ to the hypothetical line that crosses the vertebral corner/ (B) Marginal syndesmophytes: vertebral ossifications/calcification/bony outgrowth arising from the edge of the vertebral body vertically, having an angle of $\leq 45°$ to the hypothetical line that crosses the vertebral corner. (C) Non-marginal (Para-marginal) syndesmophytes: asymmetrical, thick and bulky ossifications/calcification/bony outgrowth arising from away from the edge of the vertebral body. (D) DISH: Flowing ossifications and/or calcifications of the anterior longitudinal ligament.

arthropathies, particularly PsA of the hand [65]. Especially with the ageing population, it may be complicated during the disease course to differentiate OA changes from SpA progression.

It is important to emphasize that the radiographic features of spinal NBF are not meant to be diagnostic for any disease as a stand-alone modality but rather be complimentary to the clinical features as well as other radiographic features- such as the sacroiliac joint findings. One key element to be able to differentiate the various NBF types lies under the recognition of which anatomical structures are getting ossified: Syndesmophytes are the ossification process of the annulus fibrosus, whereas para-syndesmophytes involve the soft tissues around the vertebral corners. The 'flowing ossification' in DISH mainly includes the ossification of the anterior longitudinal ligament, leading to a more widespread process exceeding the vertebral corners. An illustration of a variety of NBF types is provided in Fig. 2 with corresponding examples of the radiographs.

The major limitation of this study is having only focused on plain radiographic definitions, excluding definitions identified by computed tomography and magnetic resonance imaging. While more advanced imaging techniques can certainly be important in differentiating different types of NBF, plain films balance both cost-effectiveness and radiation exposure for patients followed over time.

We propose that the description of NBF in DISH, SpA and OA needs to include a detailed description of the anatomical location, highlight the differences in different levels of the spine and include how to differentiate DISH from syndesmophytes seen in the context of PsA and other axial SpA well as the 'tractions spurs' or osteophytes in OA. The detailed findings from the literature will allow us to propose the definitions and conduct a Delphi exercise with a group of international experts to be able to create formal NBF definitions for disease groups.

The improved ability to differentiate these conditions radiographically will not only allow the clinicians to accurately approach their patients but also will help the researchers to better classify patient phenotypes and focus on accurate radiographic outcomes.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Disclosure statement: S.Z.A. received honoraria from Abbvie, Celgene, UCB, Novartis, Jannsen, Pfizer and Sanofi. The other authors have disclosed no conflicts of interest.

Acknowledgment

Dr. Ozun Bayindir Tsechelidis and Dr. Ricardo Sabido-Sauri contributed to this manuscript for review and data extraction at the stage of revision.

References

1. de Vlam K, Lories RJ, Luyten FP. Mechanisms of pathologic new bone formation. Curr Rheumatol Rep 2006;8:332–7.
2. Lories RJ, Luyten FP, de Vlam K. Progress in spondylarthritis. Mechanisms of new bone formation in spondyloarthritis. Arthritis Res Ther 2009;11:221.
3. Appel H, Maier R, Loddenkemper C *et al.* Immunohistochemical analysis of osteoblasts in zygapophyseal joints of patients with ankylosing spondylitis reveal repair mechanisms similar to osteoarthritis. J Rheumatol 2010;37:823–8.
4. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology 1976;119:559–68.
5. Haddad A, Thavaneswaran A, Toloza S, Chandran V, Gladman DD. Diffuse idiopathic skeletal hyperostosis in psoriatic arthritis. J Rheumatol 2013;40:1367–73.
6. Kuperus JS, Waalwijk JF, Regan EA *et al.* Simultaneous occurrence of ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis: a systematic review. Rheumatology (Oxford) 2018; 57:2120–8.
7. Pappone N, Di Minno MND, Iervolino S *et al.* The impact of concomitant diffuse idiopathic skeletal hyperostosis on the achievement of minimal disease activity in subjects with psoriatic arthritis. Rheumatol Int 2015;35:2041–6.
8. Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Res Ther 2017;19:18.
9. Riley MJ, Ansell BM, Bywaters EG. Radiological manifestations of ankylosing spondylitis according to age at onset. Ann Rheum Dis 1971;30:138–48.
10. Gonzalez-Lopez L, Fajardo-Robledo NS, Miriam Saldaña-Cruz A *et al.* Association of adipokines, interleukin-6, and tumor necrosis factor-alpha concentrations with clinical characteristics and presence of spinal syndesmophytes in patients with ankylosing spondylitis: a cross-sectional study. J Int Med Res 2017; 45:1024–35.
11. Gamez-Nava JI, de la Cerda-Trujillo LF, Vazquez-Villegas ML et al Association between bone turnover markers, clinical variables, spinal syndesmophytes and bone mineral density in Mexican patients with ankylosing spondylitis. Scand J Rheumatol 2016; 45:480–90.
12. Reijnierse M. Radiographic/MR imaging correlation of paravertebral ossifications in ligaments and bony vertebral outgrowths: anatomy, early detection, and clinical impact. Magn Reson Imaging Clin N Am 2019;27:641–59.
13. Braun J, Baraliakos X, Regel A, Kiltz U. Assessment of spinal pain. Best Pract Res Clin Rheumatol 2014;28:875–87.
14. Mattar M, Salonen D, Inman RD. Imaging of spondyloarthropathies. Rheum Dis Clin North Am 2013;39:645–67.
15. Olivieri I, D'Angelo S, Palazzi C, Padula A. Spondyloarthritis and diffuse idiopathic skeletal hyperostosis: two different diseases that continue to intersect. J Rheumatol 2013;40:1251–3.
16. Ostergaard M. Can imaging be used for inflammatory arthritis screening? Semin Musculoskelet Radiol 2012;16:401–9.
17. Braum L, Hermann KGA. Utility of imaging in the diagnosis and assessment of axial spondyloarthritis. Int J Adv Rheumatol 2010; 8:127–35.
18. Olivieri I, D'Angelo S, Palazzi C *et al.* Diffuse idiopathic skeletal hyperostosis: differentiation from ankylosing spondylitis. Curr Rheumatol Rep 2009;11:321–8.
19. Resnick D. Inflammatory disorders of the vertebral column: seronegative spondyloarthropathies, adult-onset rheumatoid arthritis, and juvenile chronic arthritis. Clin Imaging 1989; 13:253–68.
20. Kerr R, Resnick D. Radiology of the seronegative spondyloarthropathies. Clin Rheum Dis 1985;11:113–46.
21. Baraliakos X. Imaging in axial spondyloarthritis. Isr Med Assoc J 2017;19:712–8.
22. Petcharat C, Srinonprasert V, Chiowchanwisawakit P. Association between syndesmophyte and metabolic syndrome in patients with psoriatic arthritis or ankylosing spondylitis: a cross-sectional study. BMC Musculoskelet Disord 2021;22:367.
23. Maejima H, Taniguchi T, Watarai A, Aki R, Katsuoka K. Analysis of clinical, radiological and laboratory variables in psoriatic arthritis with 25 Japanese patients. J Dermatol 2010;37:647–56.
24. Chandran V, Barrett J, Schentag CT, Farewell VT, Gladman DD. Axial psoriatic arthritis: update on a longterm prospective study. J Rheumatol 2009;36:2744–50.
25. Helliwell PS, Hickling P, Wright V. Do the radiological changes of classic ankylosing spondylitis differ from the changes found in the spondylitis associated with inflammatory bowel disease, psoriasis, and reactive arthritis? Ann Rheum Dis 1998;57:135–40.
26. Hanly JG, Russell ML, Gladman DD. Psoriatic spondyloarthropathy: a long term prospective study. Ann Rheum Dis 1988; 47:386–93.
27. Eshed I, Hermann KA, Zejden A, Sudol-Szopinska I. Imaging to differentiate the various forms of seronegative arthritis. Semin Musculoskelet Radiol 2018;22:189–96.
28. Taylor WJ, Porter GG, Helliwell PS. Operational definitions and observer reliability of the plain radiographic features of psoriatic arthritis. J Rheumatol 2003;30:2645–58.
29. Sudoł-Szopińska I, Matuszewska G, Kwiatkowska B, Pracoń G. Diagnostic imaging of psoriatic arthritis. Part I: etiopathogenesis, classifications and radiographic features. J Ultrason 2016; 16:65–77.
30. Spadaro A, Lubrano E. Psoriatic arthritis: imaging techniques. Reumatismo 2012;64:99–106.
31. Klecker RJ, Weissman BN. Imaging features of psoriatic arthritis and Reiter's syndrome. Semin Musculoskelet Radiol 2003; 7:115–26.
32. Porter GG. Psoriatic arthritis. Plain radiology and other imaging techniques. Baillieres Clin Rheumatol 1994;8:465–82.
33. Bazzocchi A, Aparisi Gomez MP, Guglielmi G. Conventional radiology in spondyloarthritis. Radiol Clin North Am 2017; 55:943–66.
34. Ory PA. Radiography in the assessment of musculoskeletal conditions. Best Pract Res Clin Rheumatol 2003;17:495–512.
35. de Bruin F, ter Horst S, Bloem HL *et al.* Prevalence of degenerative changes of the spine on magnetic resonance images and radiographs in patients aged 16-45 years with chronic back pain of short duration in the Spondyloarthritis Caught Early (SPACE) cohort. Rheumatology (Oxford) 2016;55:56–65.
36. Baraliakos X, Heldmann F, Callhoff J *et al.* Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis 2014;73:1819–25.
37. Baraliakos X, Listing J, Buschmann J, von der Recke A, Braun J. A comparison of new bone formation in patients with ankylosing spondylitis and patients with diffuse idiopathic skeletal hyperostosis: a retrospective cohort study over six years. Arthritis Rheum 2012;64:1127–33.
38. Baraliakos X, Listing J, Rudwaleit M *et al.* Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. Ann Rheum Dis 2007; 66:910–5.
39. Schueller-Weidekamm C, Mascarenhas VV, Sudol-Szopinska I et al Imaging and interpretation of axial spondylarthritis: the radiologist's perspective—consensus of the Arthritis Subcommittee of the ESSR. Semin Musculoskelet Radiol 2014;18:265–79.
40. Lubrano E, Marchesoni A, Olivieri I *et al.* The radiological assessment of axial involvement in psoriatic arthritis. J Rheumatol Suppl 2012;89:54–6.

41. Arlet J, Mazieres B. [Hyperostotic disease]. Rev Med Interne 1985; 6:553–64.
42. Brigode M, Francois RJ, Dory MA. Radiological study of the sacroiliac joints in vertebral ankylosing hyperostosis. Ann Rheum Dis 1982;41:225–31.
43. Forestier J, Lagier R. Ankylosing hyperostosis of the spine. Clin Orthop Relat Res 1971;74:65???83–83.
44. Julkunen H, Heinonen OP, Knekt P, Maatela J. The epidemiology of hyperostosis of the spine together with its symptoms and related mortality in a general population. Scand J Rheumatol 1975; 4:23–7.
45. Marcelli C, Yates AJ, Barjon MC *et al.* Pagetic vertebral ankylosis and diffuse idiopathic skeletal hyperostosis. Spine (Phila Pa 1976) 1995;20:454–9.
46. Guo B, Jaovisidha S, Sartoris DJ *et al.* Correlation between ossification of the stylohyoid ligament and osteophytes of the cervical spine. J Rheumatol 1997;24:1575–81.
47. Denko CW, Boja B, Malemud CJ. Growth hormone and insulin-like growth factor-I in symptomatic and asymptomatic patients with diffuse idiopathic skeletal hyperostosis (DISH). Front Biosci 2002;7:a37–43.
48. Rogers J, Waldron T, Dieppe P, Watt I. Arthropathies in palaeopathology: the basis of classification according to most probable cause. J Archaeol Sci 1987;14:179–93.
49. Forestier J, Rotes-Querol J. Senile ankylosing hyperostosis of the spine. Ann Rheum Dis 1950;9:321–30.
50. Resnick D, Shaul SR, Robins JM. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier's disease with extraspinal manifestations. Radiology 1975;115:513–24.
51. Middleton K, Fish DE. Lumbar spondylosis: clinical presentation and treatment approaches. Curr Rev Musculoskelet Med 2009; 2:94–104.
52. Okpala FO. Comparison of Four Radiographic Angular Measures of Lumbar Lordosis. J Neurosci Rural Pract 2018; 9:298–304.
53. Pfirrmann CW, Resnick D. Schmorl nodes of the thoracic and lumbar spine: radiographic-pathologic study of prevalence, characterization, and correlation with degenerative changes of 1,650 spinal levels in 100 cadavers. Radiology 2001;219:368–74.
54. Pitkanen MT, Manninen HI, Lindgren KA *et al.* Segmental lumbar spine instability at flexion-extension radiography can be predicted by conventional radiography. Clin Radiol 2002;57:632–9.
55. Gallucci M, Limbucci N, Paonessa A, Splendiani A. Degenerative disease of the spine. Neuroimaging Clin N Am 2007; 17:87–103.
56. Sieper J, Appel H, Braun J, Rudwaleit M. Critical appraisal of assessment of structural damage in ankylosing spondylitis: implications for treatment outcomes. Arthritis Rheum 2008;58:649–56.
57. Maksymowych WP, Morency N, Conner-Spady B, Lambert RG. Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. Ann Rheum Dis 2013;72:23–8.
58. Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms. Nat Rev Rheumatol 2013;9:741–50.
59. Ramos-Remus C, Gomez-Vargas A, LeClercq S, Russell AS. Radiologic features of DISH may mimic ankylosing spondylitis. Clin Exp Rheumatol 1993;11:603–8.
60. Mader R, Sarzi-Puttini P, Atzeni F *et al.* Extraspinal manifestations of diffuse idiopathic skeletal hyperostosis. Rheumatology (Oxford) 2009;48:1478–81.
61. Maertens M, Mielants H, Verstraete K, Veys EM. Evaluation of the involvement of axial entheses and sacroiliac joints in relation to diagnosis: comparison among diffuse idiopathic skeletal hyperostostis (DISH), osteoarthrosis and ankylosing spondylitis. Clin Rheumatol 1992;11:551–7.
62. Oudkerk SF, de Jong PA, Attrach M *et al.* Diagnosis of diffuse idiopathic skeletal hyperostosis with chest computed tomography: inter-observer agreement. Eur Radiol 2017;27:188–94.
63. McGonagle D, Hermann KG, Tan AL. Differentiation between osteoarthritis and psoriatic arthritis: implications for pathogenesis and treatment in the biologic therapy era. Rheumatology (Oxford) 2015;54:29–38.
64. Menz HB, Marshall M, Thomas MJ *et al.* Associations Between Calcaneal Enthesophytes and Osteoarthritis of the Hands and Feet. Arthritis Care Res (Hoboken) 2020;72:1343–8.
65. Punzi L, Ramonda R, Sfriso P. Erosive osteoarthritis. Best Pract Res Clin Rheumatol 2004;18:739–58.
66. Jaovisidha S, Techatipakorn S, Apiyasawat P *et al.* Degenerative disk disease at lumbosacral junction: plain film findings and related MRI abnormalities. J Med Assoc Thai 2000;83:865–71.
67. Katevuo K, Aitasalo K, Lehtinen R, Pietila J. Skeletal changes in dentists and farmers in Finland. Community Dent Oral Epidemiol 1985;13:23–5.

Rheumatology Advances in Practice, 2024, 8, 1–11
https://doi.org/10.1093/rap/rkae061
Systematic Review and Meta-Analysis