Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms

Reuven Mader, Jorrit-Jan Verlaan and Dan Buskila

Abstract | Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic condition characterized by the ossification and calcification of ligaments and entheses. DISH is observed on all continents and in all races, but most commonly in men over 50 years of age. Although DISH is asymptomatic in most individuals, the condition is often an indicator of underlying metabolic disease, and the presence of spinal or extraspinal ossifications can sometimes lead to symptoms including pain, stiffness, a reduced range of articular motion, and dysphagia, as well as increasing the risk of unstable spinal fractures. The aetiology of DISH is poorly understood, and the roles of the many factors that might be involved in the development of excess bone are not well delineated. The study of pathophysiological aspects of DISH is made difficult by the formal diagnosis requiring the presence of multiple contiguous fully formed bridging ossifications, which probably represent advanced stages of DISH. In this Review, the reader is provided with an up-to-date discussion of the epidemiological, aetiological and clinical aspects of DISH. Existing classification criteria (which, in the absence of diagnostic criteria, are used to establish a diagnosis of DISH) are also considered, together with the need for modified criteria that enable timely identification of early phases in the development of DISH.

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Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a poorly understood, systemic condition characterized by progressive calcification and ossification of ligaments and entheses. Although the first description of DISH (by Forestier and Rotes-Querol using the dated term 'ankylosing hyperostosis') dates back to 1950,[1] a large body of evidence shows DISH to be of more ancient origin.[2] The formal diagnosis of DISH is established when simple descriptive morphological abnormalities of the thoracic spine are observed radiologically (Figure 1). Several names have been previously proposed for the collection of these features, including senile vertebral ankylosing hyperostosis, spondylitis deformans, spondylosis hyperostotica and spondylitis ossificans ligamentosa.[3] However, the generally accepted current name—diffuse idiopathic skeletal hyperostosis—better reflects the systemic nature of the condition and the paucity of knowledge regarding its aetiology.

Because DISH is a largely asymptomatic condition, with most affected individuals not aware of its presence, it has not received much attention from clinicians and researchers. In addition, some studies have suggested that DISH is of little clinical relevance.[4] Increasing evidence, however, shows DISH to be an indicator for a number of pathological conditions. The presence of DISH may indicate underlying metabolic derangement and is associated with cardiovascular disease.[5] Moreover, as a direct consequence of DISH, bone depositions may lead to biomechanical changes of the musculoskeletal system and/or the formation of obstructive cervical masses.[6,7] In this Review, the current understanding of DISH is discussed with a special focus on epidemiology, aetiology, clinical manifestations and treatment options. Furthermore, the present criteria for the definition of DISH are scrutinized, and suggestions for a new and improved version proposed.

Epidemiology

Historical notes

Macroscopic examinations of skeletal remains from humans living in medieval and more ancient times show DISH to be particularly prevalent in individuals of high social status, even when taking into account the longevity of elite groups.[8,9] Features suggestive of DISH have also been found in the skeleton of the Egyptian pharaoh Ramses II and in Neanderthals living 50,000 years ago.[10,11] Factors suggested to have contributed to the development of DISH in privileged ancient individuals include a protein-rich diet, sedentary work and obesity.[12] The marked prevalence of DISH in medieval clergymen prompted some authors to relate the development of DISH to 'a monastic way of life' and view it as an 'occupational disease'.[13,14] However, as criteria to establish the diagnosis of DISH have not always been applied uniformly (currently the classification by Resnick *et al.*[3] from 1976 is most commonly used to define the disease), some caution is advised when

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Key points

- Diffuse idiopathic skeletal hyperostosis (DISH) is characterized by entheseal ossification and/or calcification involving mainly the thoracic spine
- Peripheral joints and adjacent entheses can also be involved
- The pathogenesis of DISH is not clear, but several factors may promote the differentiation of mesenchymal cells into bone-forming cells
- DISH is often associated with a variety of metabolic derangements, which may increase cardiovascular morbidity
- Patients with DISH also have an increased risk of complicated spinal fractures, with associated morbidities

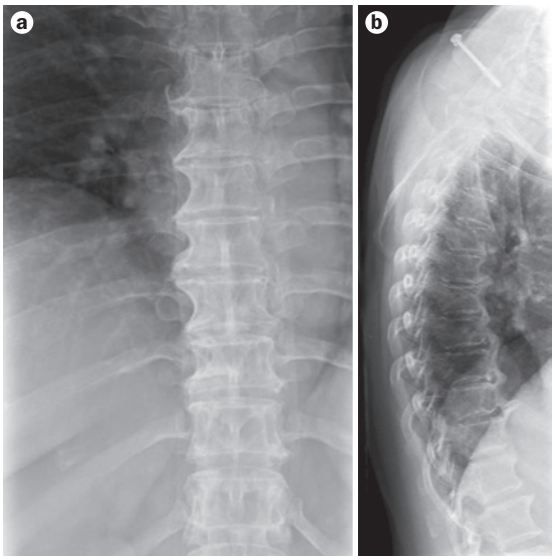

Figure 1 | The characteristic radiological features of DISH. **a** | Right-sided flowing osteophytes connecting thoracic vertebrae. **b** | Ossification of the anterior longitudinal ligament. Abbreviation: DISH, diffuse idiopathic skeletal hyperostosis.

comparing the results from older studies. Some historical studies tentatively link DISH to physical impairment, although these reports must be regarded as of mainly anecdotal value.[9,15]

Modern era

Epidemiological data published in the past three decades show DISH to be most prevalent in developed countries,[16] although this apparent predominance might be due to the more frequent use of advanced radiological examinations in these countries than in others. The condition is unequally distributed between males and females (in a ratio of ~2:1), and its prevalence rapidly increases with age.[17] In an epidemiological outpatient study, Weinfeld and colleagues found the prevalence of DISH in patients over 50 years of age to be 25% for males and 15% for females.[18] A study aiming to find the prevalence of DISH in the Netherlands by screening 501 chest radiographs obtained for unrelated medical conditions corroborated these results (17% of the individuals over the age of 50 years in this study had DISH) and demonstrated that male gender and advancing age increase the probability of the development of DISH.[17] Although DISH is more frequently observed in Western societies than elsewhere, publications have confirmed its presence across all continents (Antarctica excluded).[7]

As the natural course of DISH is typically benign, most individuals affected do not seek medical help, and the diagnosis is often established during the work-up for other medical conditions.[19] A reliable estimation of the prevalence of DISH for a general population is therefore not possible. Despite this lack of definitive baseline data, some researchers predict a steep increase in the prevalence of DISH in Western countries, owing to the widespread presence of risk factors for its development, notably obesity, diabetes mellitus, hypertension and increased life expectancy.[20,21]

Clinical manifestations

Spinal involvement

Radiological characteristics

DISH is a condition that mainly affects the elderly population. DISH has some peculiarities that allow its characterization as a distinct clinical entity and differentiate it from spondylosis.[22] First, unlike spondylosis, DISH frequently (and to date by definition) involves the thoracic spine, which is not usually involved in spondylosis until late stages. Second, the intervertebral disc height is usually preserved in patients with DISH, whereas it is reduced in individuals with spondylosis.[3] These differences are probably a result of the different targets of the pathological processes. Indeed, in spondylosis, the main target is the cartilage of the intervertebral discs, whereas in DISH the target is the enthesis (with sparing of the intervertebral discs).[3,23] Third, the osteophytes in spondylosis are usually transverse, whereas the osteophytes in DISH are coarse, vertical and bridging. Last, involvement of the mobile cervical and lumbar spine in spondylosis is usually limited to the lower portions of these segments, whereas in DISH the involvement is more extensive and can be associated with various complications.[24,25] Intervertebral disc lesions are as frequent in patients with DISH as in patients with other conditions; however, they tend to occur at an earlier age in patients with DISH.[26]

Pain and impaired mobility

Whether the radiographic spinal features of DISH described above result in clinical symptoms remains a matter of controversy, to the extent that some clinicians have considered DISH to be a state and not a disease.[27] DISH was reported to be associated with morning stiffness and spinal pain in over two-thirds of 200 patients with the condition. In addition, a reduced range of motion was described in nearly half of 21 patients.[28,29] Furthermore, a study that examined the clinical features of DISH reported that the degree of pain and disability in these patients was higher than in healthy individuals, and was similar to that of patients with spondylitis.[30] By contrast, another study reported that the radiological findings of DISH are not associated with an increased frequency of pain and, in the absence of complications, have no clinical relevance.[31] In addition, a study of self-reported back pain in individuals with and without DISH suggested that the frequency of pain was actually

reduced in patients with DISH.[19] It was shown, however, that 87 patients with DISH had more soft tissue tenderness and a lower functional status than 65 control patients without DISH.[32]

The abundance of new bone formation that occurs in DISH might be responsible for stiffening of the spine (and of peripheral joints; see below) to the extent that patients with DISH can assume the stooped postural abnormalities typically observed in ankylosing spondylitis (AS), which can lead to an erroneous diagnosis of AS instead of DISH.[33] Interestingly, both DISH and AS are characterized by ossification of spinal entheses, and the mean yearly rate of progression of new bone formation in patients with DISH, in the cervical and lumbar spine, is similar to that of patients with AS.[34]

Although the thoracic spine is characteristically affected by DISH, the spinal involvement of the condition is not limited to this region. Indeed, large protruding cervical enthesophytes can develop in patients with DISH, and can cause severe complications, such as dysphagia, myelopathy, aspiration pneumonia, oesophageal obstruction, stridor, hoarseness and thoracic outlet syndrome.[25] Such enthesophytes can also make endotracheal and endoscopic procedures difficult.[25] In the lumbar spine, the large enthesophytes can be bilateral and, together with the excessive bone formation, can result in spinal stenosis.[35,36] Spinal stenosis can manifest itself as cervical myelopathy or lumbar radiculopathy, often with radicular claudication.

Fracture risk

The presence of deformable and articulating structures in spinal segments (that is, the intervertebral disc and facet joints) enables the healthy spinal column to flex, extend and rotate in reaction to muscle contractions and external force. The energy experienced during a traumatic impact is normally distributed over multiple mobile segments, and luxations (dislocations) of the spine are therefore rare occurrences.[37] In the ankylosed spine, however, energy cannot be distributed over multiple levels and, as a consequence, the spinal column in patients with DISH may fracture in a pattern similar to that observed in a long bone.[38] The number of consecutively fused spinal levels determines the length of the 'lever arm' on which traumatic forces can act. Long lever arms can lead to grossly displaced spinal fractures after a relatively minor trauma, such as a fall from a standing or sitting position or a low-speed motor vehicle collision (Figure 2).[39]

Besides displacement of spinal fractures, several studies have demonstrated that patients with fractures of the ankylosed spine (due to DISH or AS) have a twofold to fivefold higher risk of neurological deficits on hospital admission than patients with non-ankylosed spine fractures.[37–40] Furthermore, patients admitted with fractures of the ankylosed spine were shown to have two times as many secondary neurological deficits (often due to a failure to recognize the presence of a fracture or a failure to properly immobilize the fractured spine), almost two times as many complications, and a threefold to fivefold increase in mortality rate.[39,41] Therefore, in patients screened for traumatic injuries of the spinal column, however minor, the presence of spinal ankylosis on radiographs (due to AS or DISH) should lead to a high index of suspicion for unstable fractures, loss of function and an increased risk for unfavourable outcome.

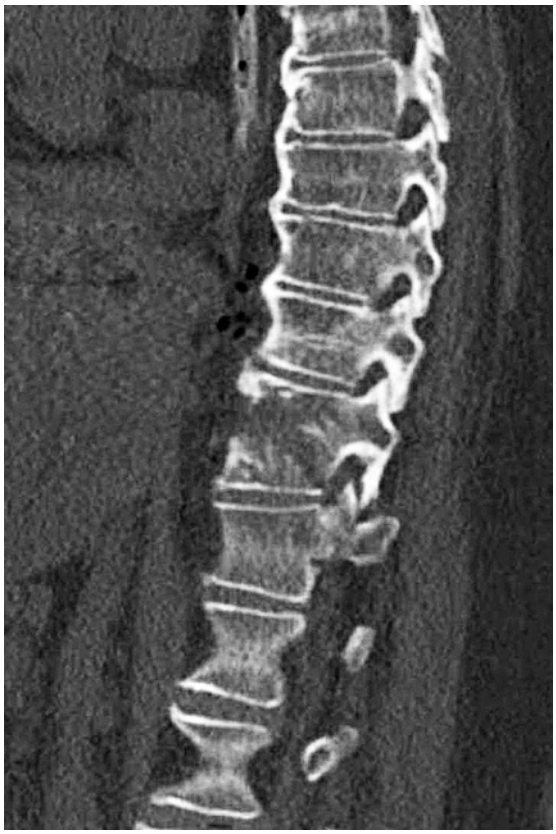

Figure 2 | A typical spinal fracture in a patient with DISH. The sagittal computed tomography image of the thoracic spine of a 68-year-old female victim of a traffic accident shows ossification of the anterior longitudinal ligament and a hyperextension-type fracture. Abbreviation: DISH, diffuse idiopathic skeletal hyperostosis.

Extraspinal involvement

The manifestations of DISH are not limited to the spine, and peripheral joints and entheses are often affected.[4,42–45] Indeed, entheseal ossification and/or calcification in the proximity of peripheral joints, for example in tendons, ligaments and the joint capsule, can be observed in patients with DISH. Owing to the age of the affected populations, DISH commonly coexists with osteoarthritis (OA), which is characterized by joint-space narrowing, subchondral sclerosis and osteophyte formation. However, it has been suggested that the involvement of peripheral joints that are commonly affected by OA is characterized in DISH by more prominent hypertrophic changes than those observed in OA, which leads to a reduced range of motion in these joints. Furthermore, OA-like changes associated with DISH can involve joints not usually affected by OA, such as the metacarpophalangeal joints, elbow, shoulder and ankle.[4,42–45] These features probably result from the ossification and calcification of entheses adjacent to joints.

One unanswered question is what effect these changes have on the clinical presentation of DISH. It could be assumed that damaged joints with OA-like lesions will be painful. However, few controlled studies have been conducted to assess pain in hyperostotic peripheral joints, and they have yielded conflicting results. For example, elbow pain was only slightly more prevalent in patients with hyperostosis of the elbow ($n = 48$) than in controls without elbow hyperostosis ($n = 24$); thus, this radiological finding was considered to be of questionable clinical relevance.[4] By contrast, the same group of investigators concluded that shoulder hyperostosis in patients with DISH is a potential cause of pain.[43] Thus, although the clinical impact of hyperostosis in peripheral joints is not yet clear, limited range of motion and pain in OA-atypical sites may draw attention to the possibility of DISH.

As mentioned above, calcification and ossification of peripheral entheses, such as those in the heel, ribs and pelvis, have been frequently observed in patients with DISH.[46,47] Although some physicians have suggested the inclusion of symmetrical large enthesophytes in the classification of DISH, no studies have validated this proposal.[12,28] The clinical significance of these enthesopathies is not clear, although in our experience the entheses can become tender and swollen. In a comparison of abnormalities at 14 pelvic sites in patients with DISH ($n = 93$) versus patients with moderate to severe spondylosis, ossification of the iliolumbar, sacrotuberous, and sacroiliac ligaments, with enthesophytic overgrowth at the lesser trochanter, proved to be significant in distinguishing between these entities.[48]

Heterotopic ossification

Reflecting the systemic bone-forming nature of the disease, patients with DISH have a greater propensity than control individuals to develop heterotopic ossifications in response to local events, including joint replacement surgery.[24] In some cases, these ossifications can impair the proper functioning of the affected joint, and prophylactic treatment with irradiation or NSAIDs is indicated in these patients. It is currently not known what causes the formation of heterotopic ossifications, although some physicians have speculated, having observed the reoccurrence of these ossifications after surgical resection, that the surgical trauma itself induces ossification through as yet unknown pathways.[49]

Aetiology and pathogenesis

The aetiology and pathogenesis of DISH are far from clear. However, DISH has to be considered a bone-forming disease. Indeed, the hallmark of the condition is new bone formation, in bones and especially in entheses. The enthesis is composed of fibroblasts, chondrocytes, collagen fibres and calcified matrix; these components might be influenced by various mediators that can promote new bone formation in these sites.

Genetic factors

The variation in the prevalence of DISH throughout the world suggests that genetic factors might play a part in its pathogenesis. Moreover, familial clustering of the condition and early onset (in the third decade of life) in some affected families have been observed, which are also suggestive of a genetic contribution to the disease.[50,51] Studies in dogs have revealed the overall prevalence of canine DISH to be 3.8%, whereas in the Boxer breed it is >40%, which further supports the existence of a genetic component in the risk of developing DISH.[52] So far, however, only one potential susceptibility gene (namely *COL6A1*, which encodes type VI collagen α chain) has been identified.

Single nucleotide polymorphisms in *COL6A1* have been reported in Japanese but not Czech patients with DISH.[53,54] *COL6A1* is also a known susceptibility gene for ossification of the posterior longitudinal ligament (OPLL), a disorder that is closely associated with and can coexist with DISH. OPLL usually involves the cervical spine and, similarly to DISH, it affects the elderly, more often males, and has been reported to be associated with low glucose tolerance and obesity.[55] Nonetheless, the association between *COL6A1* variants and DISH was stronger among patients with DISH without OPLL than in patients with concomitant DISH and OPLL, suggesting that OPLL associated with DISH might differ from the common form of isolated OPLL.

The protein encoded by *COL6A1*, type VI collagen α chain, is an extracellular matrix protein that might serve as a scaffold for osteoblastic or pre-osteoblastic cells or chondrocytes that subsequently proceed to membranous or endochondral ossification.[54] Thus, although the effects of *COL6A1* variants on bone metabolism have not been elucidated, it has been suggested that this protein might be involved in ectopic bone formation in DISH and OPLL.

Metabolic factors

Although DISH is a musculoskeletal condition, it has to be viewed as a systemic disease and has often been linked to metabolic and constitutional factors, many of which form part of the metabolic syndrome.[5] Indeed, DISH has been reported to be associated with obesity, high waist-to-hip circumference ratio, dyslipidemia, hypertension, glucose intolerance, type 2 diabetes, hyperuricaemia, hyperinsulinaemia and possibly elevated growth hormone and insulin-like growth factor 1 (IGF-1) levels.[56–61] Owing to these metabolic derangements, patients with DISH have an increased likelihood of being affected by metabolic syndrome and an increased risk for the development of coronary artery disease and stroke.[5,62]

Excess body weight has been reported in patients with DISH since the early description by Forestier,[1] and this finding has been reiterated in other studies.[30,63] Moreover, DISH has been associated with type 2 diabetes,[60] although other investigators have questioned the association.[64] Both excess body weight and type 2 diabetes are often accompanied by hyperinsulinaemia, which has also been reported in patients with DISH.[56–58,65–67] Insulin has been shown to promote the differentiation of mesenchymal cells into chondrocytes *in vitro*,[68] suggesting that

hyperinsulinaemia might induce chondrogenesis and possibly subsequent ossification in ligaments (Figure 3).[59]

Growth hormone and IGF-1

Growth hormone has the ability to promote bone formation, either directly by stimulating osteoblast proliferation or indirectly by promoting local IGF-1 production.[61,69] IGF-1 mediates the actions of growth hormone on bone by stimulating the proliferation of fibroblasts and chondrocytes.[70] A study of 55 patients with DISH, who were matched for age, sex, race, height and weight to 54 control individuals and 63 patients with OA, suggested that patients with DISH have a statistically significant increase in serum levels of growth hormone compared with controls, but similar levels to patients with OA.[57] Patients with DISH also have higher growth hormone levels in their synovial fluid than in their serum.[71] Intra-erythrocyte growth hormone levels might also be higher than serum levels, although it is not clear whether the transport and release of growth hormone by erythrocytes affects bone physiology.[72,73] Nonetheless, the anterior longitudinal ligament and the vertebral bodies in DISH have been shown to have increased markers of vascular supply (increased numbers of nutrient foramina), and thus it has been suggested that increased amounts of various growth factors, such as growth hormone, might be transported to these sites.

Vitamin A

Similarly to growth hormone, vitamin A and its derivatives have the ability to promote new bone formation. However, whether vitamin A has a role in the pathogenesis of DISH is controversial. Nonetheless, several studies have reported higher vitamin A levels in patients with DISH or have observed DISH-like manifestations in young patients treated with vitamin A or its derivatives.[74–76]

Signalling pathways

Wnt signalling

In recent years, the Wnt–β-catenin pathway has emerged as an important regulator of many aspects of bone and joint physiology. In particular, this pathway induces bone formation, both by diverting the differentiation of mesenchymal cells away from chondrocytes and adipocytes towards osteoblasts and by inhibiting osteoblast apoptosis and osteoclastogenesis. Wnt signalling can be inhibited by the endogenous secreted protein Dickkopf-related protein 1 (DKK-1; also known as Dickkopf-1), the levels of which have been investigated in patients with DISH. A small cross-sectional study failed to show differences in DKK-1 levels between people with DISH and healthy individuals.[77] However, low DKK-1 levels might have a role in the development of extensive bony spinal bridges in a subset of patients with DISH (Figure 3).[78–80]

NFκB signalling

Nuclear factor κB (NFκB) regulates the expression of several genes that are involved in the growth and division of cells, and regulates the differentiation of multipotent

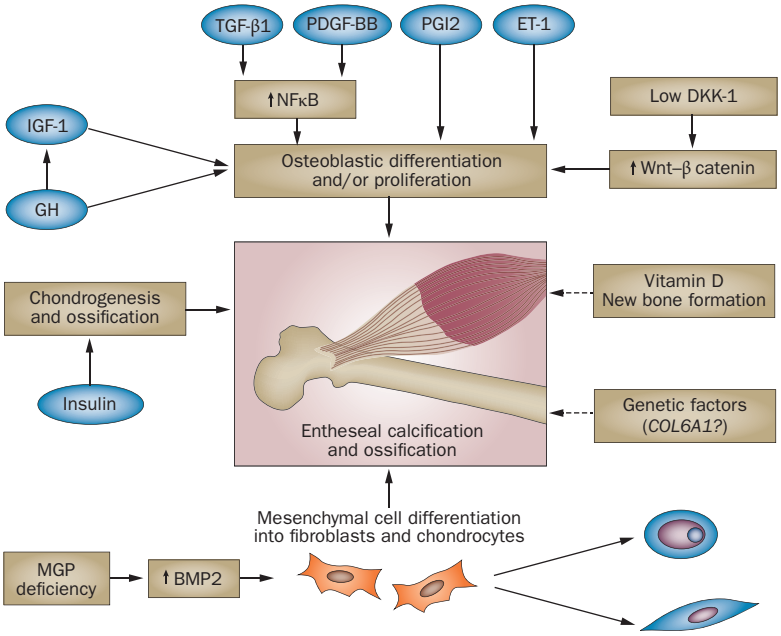

Figure 3 | Suggested factors that promote entheseal calcification and ossification in DISH. GH promotes osteoblastic differentiation and/or proliferation either directly, or indirectly by promoting IGF-1 production. NFκB activity is stimulated by PDGF-BB and TGF-β1 and promotes soft tissue ossification. ET-1 and PGI2 may promote osteoblastic differentiation. Low DKK-1 levels enhance the activity of the Wnt–β-catenin pathway, which induces osteoblastic differentiation and/or proliferation. MGP deficiency increases BMP2 activity, leading to the differentiation of mesenchymal cells into chondrocytes and fibroblasts, which may calcify. Insulin induces chondrogenesis and ossification. Abbreviations: BMP2, bone morphogenic protein 2; DISH, diffuse idiopathic skeletal hyperostosis; DKK-1, Dickkopf-related protein 1; ET-1, endothelin 1; GH, growth hormone; IGF-1, insulin-like growth factor 1; MGP, matrix Gla protein; NFκB, nuclear factor κB; PDGF-BB, platelet-derived growth factor BB; PGI2, prostaglandin I2; TGF-β1, transforming growth factor β1.

cells. In ligament mesenchymal cells, activation of NFκB is associated with osteoblastic differentiation.[81] The activity of NFκB can be stimulated by growth factors such as platelet-derived growth factor BB (PDGF-BB) and transforming growth factor β1 (TGF-β1); higher levels of these factors were observed in non-ossified ligament tissue from patients with DISH and/or ossification of the spinal ligaments than in tissue from patients with other spinal conditions.[81] This study also found increased alkaline phosphatase (ALP) activity in the ligament cells from patients with DISH and/or ossification of the spinal ligaments following *in vitro* culture, reflecting the maturation of these cells into osteoblasts.[81] These findings hint at a possible role for growth factor-induced NFκB signalling in the promotion of soft tissue ossification, although further studies are needed to confirm the relevance of the observed associations. Interestingly, both TGF-β1 levels and PDGF-BB signalling might be increased in type 2 diabetes,[82,83] which might in part explain the association between type 2 diabetes and DISH.

BMP2 signalling

Bone morphogenic protein 2 (BMP2) and its receptors participate in the ligamentous ossification process by inducing the differentiation of mesenchymal cells into

Table 1 | Suggested main diagnostic features of DISH

Definition	Number of vertebrae connected by bony bridges	Peripheral enthesopathies	SIJ involvement
Resnick and Niwayama[3]	4 in the thoracic spine	Not required	Not involved
Arlet and Mazieres[93]	3 in the lower thoracic spine	Not required	Ossification in the vicinity of the SIJ allowed
Utsinger[28]			Involvement of the SIJ is not an exclusion criterion
Definite DISH	4 in the thoracolumbar spine	Not required	
Probable DISH	2 in the thoracolumbar spine	Bilateral enthesopathies	
Possible DISH	2 in the thoracolumbar spine None	Not required Symmetrical enthesopathies preferably in >2 anatomical sites	
Rogers and Waldron[14]	3 in the thoracic spine	Peripheral calcification or ossification of ligaments and/or entheses	No reference

Abbreviations: DISH, diffuse idiopathic skeletal hyperostosis; SIJ, sacroiliac joint.

fibroblasts and chondrocytes and by increasing ALP activity (Figure 3).[84,85] The activity of BMP2 is inhibited by matrix Gla protein (MGP), and therefore deficiency of MGP or its defective carboxylation increases levels of active BMP2, with resultant excess new bone formation.[61,86] Upregulation of the expression of *BMP2* and *BMP4* mRNA has been observed following mechanical stress in spinal ligament cells from patients with OPLL,[87] and thus it is possible that this pathway might also be involved in the ossification process in DISH.

PGI2 and endothelin 1

Prostaglandin I2 (PGI2) is a potent inhibitor of bone resorption, and endothelin 1 is a potent vasoactive peptide that might regulate ectopic calcification of the vasculature. Besides its endothelial expression, endothelin 1 is reportedly expressed in osteocytes, osteoblasts and osteoclasts, and it may regulate the proliferation of these cells.[89,90] *In vitro* studies of cells harvested during surgery from patients with OPLL and from control individuals showed that mechanical stress on OPLL cells can enhance the production of PGI2 and endothelin 1.[88,89] Both of these molecules can induce, through various mechanisms, ALP activity and osteogenic differentiation in spinal ligament cells. Endothelin 1 can exert its activity directly by increasing the expression of osteogenic marker genes, such as those encoding ALP, type I collagen and osteocalcin. Furthermore, it can act indirectly by upregulating PGI2 expression (Figure 3).[88,89] It has been speculated that endothelin 1 and PGI2 might have roles in the pathogenesis of DISH, although this hypothesis awaits confirmation.

Vascular and mechanical factors

One of the intriguing questions about DISH is the predilection for ossification of the anterolateral aspect of the thoracic spine. Interestingly, involvement of the left side of the thoracic spine has been described in a few case reports of patients with a right-sided aorta, suggesting that aortic pulsations prevent the characteristic entheseal calcification and ossification observed in DISH.[91] In addition, the limited mobility of the thoracic spine has been suggested to be responsible for the predilection to this segment of the spine. However, a lack of mobility cannot explain the involvement of more mobile segments, such as the cervical or lumbar spine, and further studies are needed to solve this discrepancy.

Peripheral mechanisms

Mechanisms that underlie the pathogenesis of hypertrophic OA-like changes in peripheral joints and the involvement in DISH of peripheral joints not typically affected in primary OA have not been elucidated. Beyond the hyperostotic processes described above, it has been suggested that these manifestations of DISH might result from stiffening of capsules and ligaments around the joints and, as a result, increased intra-articular pressure.[92] Further research will be needed to confirm this hypothesis, as well as to elucidate the spinal mechanisms of ossification, if we are to fully understand the pathogenesis of DISH.

Diagnosis

Classification criteria

Several sets of classification criteria have been proposed for DISH (Table 1). The 1976 Resnick and Niwayama criteria[3] require either 'flowing' coarse osteophytes connecting at least four contiguous vertebrae or ossification of the anterior longitudinal ligament, together with preserved intervertebral height and an absence of apophyseal joint or sacroiliac joint (SIJ) involvement.[3] In 1985, Arlet and Mazieres[93] lowered the threshold for the number of vertebrae bridged by flowing osteophytes to three vertebrae in the lower thoracic spine. In their criteria, ossifications in the vicinity of the SIJ or iliolumbar ligament are allowed, as long as the SIJ surface is not involved.[93] Also in 1985, Utsinger further extended the classification criteria to include peripheral enthesopathies.[28] Using these criteria, a definite DISH diagnosis can be established when thoracolumbar ossification of at least four contiguous vertebrae is present; a probable diagnosis can be considered when two contiguous vertebrae are involved and bilateral peripheral enthesopathies are also observed; and a possible diagnosis can be considered either when two contiguous vertebrae are involved or when symmetrical enthesopathies

are observed in the absence of spinal involvement (in particular when they affect more than one anatomical site). The probable and possible categories may identify sets of patients who are more likely to have DISH or develop DISH later on in life, although currently there is no known established practical approach to the management of these patients. The exclusion criteria proposed by Utsinger were abnormal disc space height and apophyseal joint ankylosis.[28] Another set of classification criteria was suggested by Rogers and Waldron.[14] Again, the mandatory criteria for the diagnosis of DISH were right-sided hyperostosis of the thoracic vertebrae associated with extraspinal and/or entheseal calcification and ossification (Table 1).[14] A study of the human skeletal remains of 253 individuals found differences in the prevalence of definite DISH depending on the criteria used. The prevalence ranged from 5.5% by the Resnick criteria to 17% by the Rogers criteria. The extraspinal enthesophytes were found to be unreliable in predicting DISH.[2] None of the criteria sets used so far attempted to incorporate the constitutional and metabolic derangements reported in DISH.

Differential diagnosis

Owing to inconsistencies in the literature and a paucity of well-designed studies, no agreement has been reached regarding the incorporation of clinical symptoms, extraspinal manifestations or associated constitutional and metabolic conditions in the diagnosis of DISH.[94] Other diseases that exhibit excessive bone formation and entheseal involvement should be considered before a diagnosis of DISH is established. Being a disease most commonly observed in elderly individuals, DISH may frequently coexist with spondylosis and OA. Distinguishing between these entities is not always easy but can be achieved by considering the different spinal and extraspinal manifestations (see above). DISH also shares features with AS, including a tendency for ossification of ligaments and entheses, although in AS this process is thought to occur through different, inflammatory mechanisms. DISH can be distinguished from AS by the absence of SIJ involvement, the appearance and angle of projection from the vertebrae of the osteophytes or syndesmophytes, the older age at presentation, the absence of apophyseal joint obliteration, the lack of association with HLA-B27 and the lower degree of pain and discomfort.[6,95]

Treatment

Approach to management

Data regarding therapeutic interventions in DISH are very limited. Although patients with DISH are presumably included in OA therapeutic trials, no reported therapeutic studies have specifically focused on this group of patients. Interventions aimed at preventing the condition or arresting its progression are hampered by the long time period required for the development of the vertebral bony bridges. It has been suggested that it takes approximately 10 years from the start of the ossification to its full radiological expression.[96] In this regard, the rate of new bone formation is similar to that observed in AS.[34] Therefore, given the lack of disease-modifying therapeutics, the treatment of DISH should be directed towards the musculoskeletal manifestations, the associated metabolic and constitutional co-morbidities, and the complications of the condition (Box 1).

Box 1 | Suggested therapeutic interventions in DISH

- Weight reduction and physical activity
- Physical therapy
- Diet low in saturated fat and carbohydrate
- Instruction in joint-protection techniques
- Entheseal protection and local corticosteroid infiltration
- Local application of NSAIDs or capsaicin
- Analgesics
- Systemic NSAIDs
- Avoidance of thiazide diuretics and β-adrenergic antagonists
- Prevention of accidental falls and aspiration pneumonia
- Prevention of post-surgical heterotopic ossification
- Surgical resection of cervical osteophytes (in extreme cases)

Abbreviation: DISH, diffuse idiopathic skeletal hyperostosis.

Treatment of pain

Physical therapy to preserve mobility and alleviate pain is thought to be a reasonable approach. However, a small study on the effect of exercise therapy in patients with DISH did not show a significant improvement in the range of spinal motion, except for lumbosacral flexion.[97] A beneficial effect of chiropractic management was reported only in two case reports.[98,99] By contrast, a small uncontrolled study reported that patients with DISH who have musculoskeletal pain could benefit from treatment with NSAIDs or heat therapy.[100]

The peripheral joints in patients with DISH are affected in a similar manner to those in patients with OA (although with hypertrophic changes or the involvement of atypical sites). Therefore, given the lack of studies on the medical treatment of DISH, suggested treatments for OA can be cautiously adopted. Such approaches include evaluation of activities of daily living; instruction in joint protection techniques and use of physiotherapy; use of oral NSAIDs, analgesics, tramadol and, when there is evidence of OA lesions, chondroitin and glucosamine; and intra-articular corticosteroid injections. In patients with OA, for some joints, topical application of capsaicin and NSAIDs might be preferred over oral NSAIDs.[101] In fact, the use of locally acting NSAIDs could be as effective as systemic therapy, at least in patients with knee OA, and thus might be useful for the relief of pain in the peripheral joints and the entheses in patients with DISH.[102] Painful entheses might also benefit from soft protections or local corticosteroid injections, although no studies have yet investigated such approaches in patients with DISH.

Prevention and management of comorbidities

The metabolic and constitutional abnormalities frequently observed in patients with DISH deserve attention

for their effect on the risk of cardiovascular disease. Thus, physical activity, low intake of saturated fat and of carbohydrates, and weight reduction should be encouraged. Moreover, such strategies should help to reduce hyperinsulinaemia, which is thought to have a role in the pathogenesis of DISH. In addition, hypertensive patients with DISH should try to avoid medications that might increase insulin resistance, such as thiazide diuretics and β-adrenergic antagonists (β-blockers), and preferentially select medications that improve insulin resistance, such as angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers and α-adrenergic antagonists.[103]

Surgery and complications

In the absence of traumatic fractures, surgical spinal interventions are rarely needed in patients with DISH, except in cases with severe spinal stenosis or large cervical osteophytes. Two small case series have reported that patients with large anterior cervical osteophytes causing dysphagia or airway obstruction, who failed medical therapy, might benefit from surgical resection of the osteophytes.[104,105]

Finally, patients and physicians should be aware of, and try to prevent, complications such as aspiration pneumonia, difficulties in endotracheal intubation or upper gastrointestinal endoscopy, and accidental falls. Prevention of heterotropic ossification using NSAIDs, vitamin K antagonists or irradiation should be considered in patients undergoing orthopaedic surgery (Box 1).[106,107]

Suggestions for future research

DISH is a clinical and radiological entity usually diagnosed on radiographic grounds only. Nonetheless, DISH should be considered an extensive proliferative musculoskeletal disease associated with clinical and metabolic derangements. Owing to the limitations of the current definitions and classification criteria, the condition cannot be diagnosed in its early stages. As a result, effective treatment to arrest or slow the progression of the disease has never been investigated. We believe that large symmetrical peripheral enthesopathies (in the absence of spinal involvement) can be the only manifestation of the condition. Furthermore, very little is known about the aetiology, pathogenesis and associated conditions that, in our opinion, should be incorporated in future definitions of the disease. Thus, we think that new diagnostic criteria should be established and validated, with particular emphasis on early manifestation.

It is unlikely that the excessive bone formation can be reversed, but with more knowledge it might be prevented. To this end, large-scale epidemiological studies addressing the full clinical spectrum of DISH and its prevalence, natural course and outcome are needed. Moreover, exploration of the factors responsible for bone formation, together with familial aggregation studies and the identification of genetic markers (haplotypes) associated with DISH, might help to uncover the molecular basis of the ligamentous and entheseal ossification that characterizes the condition. Such understanding might pave the way to more targeted and effective therapies in the future. So, instead of merely symptomatic relief, future research may offer a disease-modifying therapeutic approach to patients with DISH.

Conclusions

DISH is a condition characterized by new bone formation, and constitutional and metabolic abnormalities. Little is known about its pathogenesis, and suitable therapeutic approaches are unclear. A more comprehensive definition of DISH, that preferably includes patients with early phase disease, and prospective studies in patients prone to develop the condition are needed to advance our understanding of this condition.

Review criteria

The articles cited in this Review were selected from the authors' personal library of articles on DISH. Selections were made on the basis of the expert opinions of the authors.

1. Forestier, J. & Rotes-Querol, J. Senile ankylosing hyperostosis of the spine. *Ann. Rheum. Dis.* **9**, 321–330 (1950).
2. Van der Merwe, A. E., Maat, G. J. & Watt, I. Diffuse idiopathic skeletal hyperostosis: Diagnosis in a palaeopathological context. *Homo* **63**, 202–215 (2012).
3. Resnick, D. & Niwayama, G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). *Radiology* **119**, 559–568 (1976).
4. Beyeler, C. *et al.* Diffuse idiopathic skeletal hyperostosis (DISH) of the elbow: A cause of elbow pain? A controlled study. *Br. J. Rheumatol.* **31**, 319–323 (1992).
5. Mader, R., Novofestovski, I., Adawi, M. & Lavi, I. Metabolic syndrome and cardiovascular risk in patients with diffuse idiopathic skeletal hyperostosis. *Semin. Arthritis Rheum.* **38**, 361–365 (2009).
6. Mader, R. *et al.* Extraspinal manifestations of diffuse idiopathic skeletal hyperostosis. *Rheumatology* **48**, 1478–1481 (2009).
7. Verlaan, J. J., Boswijk, F. L., de Ru, J. A., Dhert, W. J. & Oner, F. C. Diffuse idiopathic skeletal hyperostosis of the cervical spine: an underestimated cause of dysphagia and airway obstruction. *Spine J.* **11**, 1058–1067 (2011).
8. Weisz, G. M., Matucci-Cerinic, M., Lippi, D. & Albury, W. R. The ossification diathesis in the medici family: DISH and other features. *Rheumatol. Int.* **31**, 1649–1652 (2011).
9. Verlaan, J. J., Oner, F. C. & Maat, G. J. Diffuse idiopathic skeletal hyperostosis in ancient clergymen. *Eur. Spine J.* **16**, 1129–1135 (2007).
10. Chhem, R. K., Schmit, P. & Fauré, C. Did Ramesses II really have ankylosing spondylitis? A reappraisal. *Can. Assoc. Radiol. J.* **55**, 211–217 (2004).
11. Crubézy, E. & Trinkaus, E. Shanidar 1: a case of hyperostotic disease (DISH) in the middle Paleolithic. *Am. J. Phys. Anthropol.* **89**, 411–420 (1992).
12. Giuffra, V. *et al.* Diffuse idiopathic skeletal hyperostosis in the Medici, Grand Dukes of Florence (XVI century). *Eur. Spine J.* **19** (Suppl. 2), S103–S107 (2010).
13. Waldron, T. DISH at merton priory: evidence for a "new" occupational disease? *BMJ* **291**, 1762–1763 (1985).
14. Rogers, J. & Waldron, T. DISH and the monastic way of life. *Int. J. Osteoarchaeol.* **11**, 357–365 (2001).
15. Ullrich, H. [Goethe's skull and skeleton] **60**, 341–368 (2002).
16. Kiss, C. *et al.* Prevalence of diffuse idiopathic skeletal hyperostosis in Budapest, Hungary. *Rheumatology (Oxford)* **41**, 1335–1336 (2002).
17. Westerveld, L. A., van Ufford, H. M., Verlaan, J. J. & Oner, F. C. The prevalence of diffuse idiopathic skeletal hyperostosis in an outpatient population in the Netherlands. *J. Rheumatol.* **35**, 1635–1638 (2008).
18. Weinfeld, R. M., Olson, P. N., Maki, D. D. & Griffiths, H. J. The prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in two large american midwest metropolitan hospital populations. *Skeletal Radiol.* **26**, 222–225 (1997).
19. Holton, K. F. *et al.* Diffuse idiopathic skeletal hyperostosis and its relation to back pain among older men: The MrOS study. *Semin. Arthritis Rheum.* **41**, 131–138 (2011).
20. Bray, G. A. & Bellanger, T. Epidemiology, trends, and morbidities of obesity and the metabolic

syndrome. *Endocrine* **29**, 109–117 (2006).
21. Mader, R. & Lavi, I. Diabetes mellitus and hypertension as risk factors for early diffuse idiopathic skeletal hyperostosis (DISH). *Osteoarthritis Cartilage* **17**, 825–828 (2009).
22. Mader, R. Diffuse idiopathic skeletal hyperostosis: a distinct clinical entity. *Isr. Med. Assoc. J.* **5**, 506–508 (2003).
23. Fornasier, V. L., Littlejohn, G. O., Urowitz, M. B., Keystone, E. C. & Smythe, H. A. Spinal entheseal new bone formation: the early changes of spinal diffuse idiopathic skeletal hyperostosis. *J. Rheumatol.* **10**, 934–947 (1983).
24. Belanger, T. A. & Rowe, D. E. Diffuse idiopathic skeletal hyperostosis: musculoskeletal manifestations. *J. Am. Acad. Orthop. Surg.* **9**, 258–267 (2001).
25. Mader, R. Clinical manifestations of diffuse idiopathic skeletal hyperostosis of the cervical spine. *Semin. Arthritis Rheum.* **32**, 130–135 (2002).
26. Di Girolamo, C. *et al.* Intervertebral disc lesions in diffuse idiopathic skeletal hyperostosis (DISH). *Clin. Exp. Rheumatol.* **19**, 310–312 (2001).
27. Hutton, C. DISH…. a state not a disease? [editorial]. *Br. J. Rheumatol.* **28**, 277–280 (1989).
28. Utsinger, P. D. Diffuse idiopathic skeletal hyperostosis. *Clin. Rheum. Dis.* **11**, 325–351 (1985).
29. Resnick, D. *et al.* Diffuse idiopathic skeletal hyperostosis (DISH) [ankylosing hyperostosis of Forestier and Rotes-Querol]. *Semin. Arthritis Rheum.* **7**, 153–187 (1978).
30. Mata, S. *et al.* A controlled study of diffuse idiopathic skeletal hyperostosis. Clinical features and functional status. *Medicine* **76**, 104–117 (1997).
31. Schlapbach, P. *et al.* Diffuse idiopathic skeletal hyperostosis (DISH) of the spine: A cause of back pain? A controlled study. *Br. J. Rheumatol.* **28**, 299–303 (1989).
32. Mader, R. *et al.* Non articular tenderness and functional status in patients with diffuse idiopathic skeletal hyperostosis. *J. Rheumatol.* **37**, 1911–1916 (2010).
33. Olivieri, I. *et al.* Diffuse idiopathic skeletal hyperostosis may give the typical postural abnormalities of advanced ankylosing spondylitis. *Rheumatology* **46**, 1709–1711 (2007).
34. 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.* **64**, 1127–1133 (2012).
35. Belanger, T. A. & Rowe, D. E. Diffuse idiopathic skeletal hyperostosis: musculoskeletal manifestations. *J. Am. Acad. Orthop. Surg.* **9**, 258–267 (2001).
36. Laroche, M. *et al.* Lumbar and cervical stenosis. Frequency of the association, role of the ankylosing hyperostosis. *Clin. Rheumatol.* **11**, 533–535 (1992).
37. Liu, P. *et al.* Spinal trauma in mainland China from 2001 to 2007: An epidemiological study based on a nationwide database. *Spine (Phila Pa 1976)* **37**, 1310–1315 (2012).
38. Caron, T. *et al.* Spine fractures in patients with ankylosing spinal disorders. *Spine (Phila Pa 1976)* **35**, E458–E464 (2010).
39. Westerveld, L. A., Verlaan, J. J. & Oner, F. C. Spinal fractures in patients with ankylosing spinal disorders: A systematic review of the literature on treatment, neurological status and complications. *Eur. Spine J.* **18**, 145–156 (2009).
40. Whang, P. G. *et al.* The management of spinal injuries in patients with ankylosing spondylitis or diffuse idiopathic skeletal hyperostosis: A comparison of treatment methods and clinical outcomes. *J. Spinal Disord. Tech.* **22**, 77–85 (2009).
41. Westerveld, L. A., van Bemmel, J. C., Dhert, W. J., Oner, F. C. & Verlaan, J. J. Clinical outcome after traumatic spinal fractures in patients with ankylosing spinal disorders compared with control patients. *Spine J.* http://www.doi.org/10.1016/j.spinee.2013.06.038.
42. Littlejohn, J. O., Urowitz, M. B., Smythe, H. A. & Keystone, E. C. Radiographic features of the hand in diffuse idiopathic skeletal hyperostosis (DISH). *Radiology* **140**, 623–629 (1981).
43. Beyeler, C. *et al.* Diffuse idiopathic skeletal hyperostosis (DISH) of the shoulder. A cause of shoulder pain? *Br. J. Rheumatol.* **29**, 349–353 (1990).
44. Utsinger, P. D., Resnick, D. & Shapiro, R. Diffuse skeletal abnormalities in Forestier's disease. *Arch. Intern. Med.* **136**, 763–768 (1976).
45. Schlapbach, P. *et al.* The prevalence of palpable finger joints nodules in diffuse idiopathic skeletal hyperostosis (DISH). A controlled study. *Br. J. Rheumatol.* **31**, 531–534 (1992).
46. Littlejohn, J. O. & Urowitz, M. B. Peripheral enthesopathy in diffuse idiopathic skeletal hyperostosis (DISH): a radiologic study. *J. Rheumatol.* **9**, 568–572 (1982).
47. Resnick, D., Shaul, S. R. & Robins, J. M. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier's disease with extraspinal manifestations. *Radiology* **115**, 513–524 (1975).
48. Haller, J. *et al.* Diffuse idiopathic skeletal hyperostosis: diagnostic significance of radiographic abnormalities of the pelvis. *Radiology* **172**, 835–839 (1989).
49. Shehab, D., Elgazzar, A. H. & Collier, B. D. Heterotopic ossification. *J. Nucl. Med.* **43**, 346–353 (2002).
50. Gorman, C., Jawad, A. S. M. & Chikanza, I. A family with diffuse idiopathic hyperostosis. *Ann. Rheum. Dis.* **64**, 1794–1795 (2005).
51. Burges-Armas, J. *et al.* Ectopic calcification among families in the Azores: clinical and radiological manifestations in families with diffuse idiopathic skeletal hyperostosis and chondrocalcinosis. *Arthritis Rheum.* **54**, 1340–1349 (2006).
52. Kranenburg, H. C. *et al.* The dog as an animal model for DISH? *Eur. Spine J.* **19**, 1325–1329 (2010).
53. Havelka, S. *et al.* Are DISH and OPLL genetically related? *Ann. Rheum. Dis.* **60**, 902–903 (2001).
54. Tsukahara, S. *et al. COL6A1*, the candidate gene for ossification of the posterior longitudinal ligament, is associated with diffuse idiopathic skeletal hyperostosis in Japanese. *Spine* **30**, 2321–2324 (2005).
55. Shingyouchi, O., Nagahama, A. & Niida, M. Ligamentous ossification of the cervical spine in the late middle-aged Japanese men. Its relation to body mass index and glucose metabolism. *Spine* **21**, 2474–2478 (1996).
56. Littlejohn, G. O. Insulin and new bone formation in diffuse idiopathic skeletal hyperostosis. *Clin. Rheumatol.* **4**, 294–300 (1985).
57. Denko, C. W., Boja, B. & Moskowitz, R. W. Growth promoting peptides in osteoarthritis and diffuse idiopathic skeletal hyperostosis —insulin, insulin-like growth factor-I, growth hormone. *J. Rheumatol.* **21**, 1725–1730 (1994).
58. Vezyroglou, G., Mitropoulos, A., Kyriazis, N. & Antoniadis, C. A metabolic syndrome in diffuse idiopathic skeletal hyperostos: A controlled study. *J. Rheumatol.* **23**, 672–676 (1996).
59. Akune, T. *et al.* Insulin secretory response is positively associated with the extent of ossification of the posterior longitudinal ligament of the spine. *J. Bone Joint Surg.* **83A**, 1537–1544 (2001).
60. Kiss, C., Szilagyi, M., Paksy, A. & Poor, G. Risk factors for diffuse idiopathic skeletal hyperostosis: a case control study. *Rheumatology (Oxford)* **41**, 27–30 (2002).
61. Sarzi-Puttini, P. & Atzeni, F. New developments in our understanding of DISH (diffuse idiopathic skeletal hyperostosis). *Curr. Opin. Rheumatol.* **16**, 287–292 (2004).
62. Miyazawa, N. & Akiyama, I. Diffuse idiopathic skeletal hyperostosis associated with risk factors for stroke. *Spine* **31**, E225–E229 (2006).
63. Forestier, J. & Lagier, R. Ankylosing hyperostosis of the spine. *Clin. Orthop.* **74**, 65–83 (1971).
64. Sencan, D., Elden, H., Nacitrahan, V., Sencan, M. & Kaptanoglu, E. The prevalence of diffuse idiopathic skeletal hyperostosis in patients with diabetes mellitus. *Rheumatol. Int.* **25**, 518–521 (2005).
65. Denko, C. W. & Malemud, C. J. Body mass index and blood glucose: correlations with serum insulin, growth hormone, and insulin-like growth factor-1 levels in patients with diffuse idiopathic skeletal hyperostosis (DISH). *Rheumatol. Int.* **26**, 292–297 (2006).
66. Littlejohn, G. O. & Smythe, H. A. Marked hyperinsulinemia after glucose challenge in patients with diffuse idiopathic skeletal hyperostosis. *J. Rheumatol.* **8**, 965–968 (1981).
67. Eckertova, M. *et al.* Impaired insulin secretion and uptake in patients with diffuse idiopathic skeletal hyperostosis. *Endocr. Regul.* **43**, 149–155 (2009).
68. Mueller, M. B. *et al.* Insulin is essential for *in vitro* chondrogenesis of mesenchymal progenitor cells and influences chondrogenesis in a dose-dependent manner. *Int. Orthop.* **37**, 153–158 (2013).
69. Ohlsson, C., Bengtsson, B. A., Isaksson, O. G. P., Andereassen, T. T. & Slootweg, M. C. Growth hormone and bone. *Endocrine Rev.* **19**, 55–79 (1998).
70. Vetter, U. *et al.* Human fetal and adult chondrocytes. Effect of insulinlike growth factors I and II, insulin, and growth hormone on clonal growth. *J. Clin. Invest.* **77**, 1903–1908 (1986).
71. Denko, C. W., Boja, B. & Moskowitz, R. W. Growth factors, insulin-like growth factor-1 and growth hormone, in synovial fluid and serum of patients with rheumatic disorders. *Osteoarthritis Cartilage* **4**, 245–249 (1996).
72. Denko, C. W., Boja, B. & Malemud, C. J. Intra-erythrocyte deposition of growth hormone in rheumatic diseases. *Rheumatol. Int.* **23**, 11–14 (2003).
73. el Miedany, Y. M., Wassif, G. & el Baddini, M. Diffuse idiopathic skeletal hyperostosis (DISH): is it of vascular etiology? *Clin. Exp. Rheumatol.* **18**, 193–200 (2000).
74. Nesher, G. & Zuckner, J. Rheumatologic complications of vitamin A and retinoids. *Semin. Arthritis Rheum.* **24**, 291–296 (1995).
75. Abiteboul, M., Arlet J., Sarrabay, M. A., Mazières, B. & Thouvenot, J. P. Etude du metabolisme de la vitamine A au cours de la maladie hyperostosique de Forestier et Rote's-Querol. *Rev. Rhum. Ed. Fr.* **53**, 143–145 (1986).

76. Ling, T. C., Parkin, G., Islam, J., Seukeran, D. C. & Cunliffe, W. J. What is the cumulative effect of long-term, low dose isotretinoin on the development of DISH? *Br. J. Dermatol.* **144**, 630–632 (2001).
77. Aeberli, D., Schett, G., Eser, P., Seitz, M. & Villiger, P. M. Serum Dkk-1 levels of DISH patients are not different from healthy controls. *Joint Bone Spine* **78**, 422–423 (2011).
78. Daoussis, D. & Andonopoulos, A. P. The emerging role of Dickkopf-1 in bone biology: is it the main switch controlling bone and joint remodeling? *Semin. Arthritis Rheum.* **41**, 170–177 (2011).
79. Senolt, L. *et al.* Low circulating Dickkopf-1 and its link with severity of spinal involvement in diffuse idiopathic skeletal hyperostosis. *Ann. Rheum. Dis.* **71**, 71–74 (2012).
80. Mader, R. & Verlaan, J. J. Bone: Exploring factors responsible for bone formation in DISH. *Nat. Rev. Rheumatol.* **8**, 10–12 (2011).
81. Kosaka, T., Imakiire, A., Mizuno, F. & Yamamoto, K. Activation of nuclear factor κB at the onset of ossification of the spinal ligaments. *J. Orthop. Sci.* **5**, 572–578 (2000).
82. Inaba, T. *et al.* Enhanced expression of platelet-derived growth factor-β receptor by high glucose. Involvement of platelet-derived growth factor in diabetic angiopathy. *Diabetes* **45**, 507–512 (1996).
83. Pfeiffer, A., Middelberg-Bisping, K., Drewes, C. & Schatz, H. Elevated plasma levels of transforming growth factor-β1 in NIDDM. *Diabetes Care* **19**, 1113–1117 (1996).
84. Kon, T. *et al.* Bone morphogenetic protein-2 stimulates differentiation of cultured spinal ligament cells from patients with ossification of the posterior longitudinal ligament. *Calcif. Tissue Int.* **60**, 291–296 (1997).
85. Tanaka, H. *et al.* Involvement of bone morphogenic protein-2 (BMP-2) in the pathological ossification process of the spinal ligament. *Rheumatology* **40**, 1163–1168 (2001).
86. Zebboudj, A. F., Imura, M. & Bostrom, K. Matrix GLA protein, a regulatory protein for bone morphogenetic protein-2. *J. Biol. Chem.* **8**, 4388–4394 (2002).
87. Tanno, M., Furukawa, K. I., Ueyama, K., Harata, S. & Motomura, S. Uniaxial cyclic stretch induces osteogenic differentiation and synthesis of bone morphogenetic proteins of spinal ligament cells derived from patients with ossification of the posterior longitudinal ligaments. *Bone* **33**, 475–484 (2003).
88. Ohishi, H. *et al.* Role of prostaglandin I_2 in the gene expression induced by mechanical stress in spinal ligament cells derived from patients with ossification of the posterior longitudinal ligament. *J. Pharmacol. Exp. Ther.* **305**, 818–824 (2003).
89. Iwasawa, T. *et al.* Pathophysiological role of endothelin in ectopic ossification of human spinal ligaments induced by mechanical stress. *Calcif. Tissue Int.* **79**, 422–430 (2006).
90. Kasperk, C. H. *et al.* Endothelin-1 is a potent regulator of human bone cell metabolism. *Calcif. Tissue Int.* **60**, 368–374 (1997).
91. Carile, L., Verdone, F., Aiello, A. & Buongusto, G. Diffuse idiopathic skeletal hyperostosis and situs viscerum inversus. *J. Rheumatol.* **16**, 1120–1122 (1989).
92. Smythe, H. A. The mechanical pathogenesis of generalized osteoarthritis. *J. Rheumatol.* **10** (Suppl. 9), 11–12 (1983).
93. Arlet, J. & Mazieres, B. La maladie hyperostosique. *Rev. Mdd. Interne.* **6**, 553–564 (1985).
94. Mader, R. *et al.* Developing new classification criteria for diffuse idiopathic skeletal hyperostosis: back to square one. *Rheumatology (Oxford)* **52**, 326–330 (2013).
95. Olivieri, I. *et al.* Diffuse idiopathic skeletal hyperostosis: differentiation from ankylosing spondylitis. *Curr. Rheumatol. Rep.* **11**, 321–328 (2009).
96. Mader, R. Diffuse idiopathic skeletal hyperostosis: isolated involvement of cervical spine in a young patient. *J. Rheumatol.* **31**, 620–621 (2004).
97. Al-Herz, A., Snip, J. P., Clark, B. & Esdaile, J. M. Exercise therapy for patients with diffuse idiopathic skeletal hyperostosis. *Clin. Rheumatol.* **27**, 207–210 (2008).
98. Troyanovich, S. J. & Buettner, M. A structural chiropractic approach to the management of diffuse idiopathic skeletal hyperostosis. *J. Manipulative Physiol. Ther.* **26**, 202–206 (2003).
99. Roberts, J. A., Tristy, M. & Wolfe, M. A. Chiropractic management of a veteran with lower back pain associated with diffuse idiopathic skeletal hypertrophy and degenerative disk disease. *J. Chiropr. Med.* **11**, 293–299 (2012).
100. El Garf, A. & Khater, R. Diffuse idiopathic skeletal hyperostosis (DISH): a clinicopathological study of the disease pattern in Middle Eastern populations. *J. Rheumatol.* **11**, 804–807 (1984).
101. Hochberg, M. C. *et al.* American College of Rheumatology recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.* **64**, 465–474 (2012).
102. Roth, S. H. & Shainhouse, J. Z. Efficacy and safety of a topical diclofenac solution (pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized, double-blind, vehicle-controlled clinical trial. *Arch. Intern. Med.* **164**, 2017–2023 (2004).
103. Lithell, H. O. L. Effect of antihypertensive drugs on insulin, glucose, and lipid metabolism. *Diabetes Care* **14**, 203–209 (1991).
104. Carlson, M. L., Archibald, D. J., Graner, D. E. & Kasperbauer, J. L. Surgical management of dysphagia and airway obstruction in patients with prominent ventral cervical osteophytes. *Dysphagia* **26**, 34–40 (2011).
105. Urrutia, J. & Bono, C. M. Long-term results of surgical treatment of dysphagia secondary to cervical diffuse idiopathic skeletal hyperostosis. *Spine J.* **9**, e13–e17 (2009).
106. Guillemin, F., Mainard, D., Rolland, H. & Delagoutte, J. P. Antivitamin K prevents heterotopic ossification after hip arthroplasty in diffuse idiopathic skeletal hyperostosis: a retrospective study in 67 patients. *Acta Orthop. Scand.* **66**, 123–126 (1995).
107. Knelles, D. *et al.* Prevention of heterotopic ossification after total hip replacement: a prospective, randomized study using acetylsalicylic acid, indomethacin and fractional or single-dose irradiation. *J. Bone Joint Surg. Br.* **79**, 596–602 (1997).

Author contributions

All authors made substantial contributions to discussions of content, writing, and reviewing/editing the manuscript before submission. In addition, R. Mader and J.-J. Verlaan researched data for the article.