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REVIEW

Diffuse idiopathic skeletal hyperostosis (DISH): where we are now and where to go next

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ABSTRACT

Diffuse idiopathic skeletal hyperostosis (DISH) is a well-recognised entity characterised by calcifications and ossifications of the entheses affecting mainly the spine and peripheral sites. DISH is still insufficiently investigated and understood. The objective of this report is to highlight the present limitations of our understanding of the condition and suggest future research paths.

Key messages

- Although diffuse idiopathic skeletal hyperostosis is known for its radiographic characteristics, there are limited data about its clinical manifestations, aetiology, pathogenesis and treatment.
- This article highlights the limitations of our understanding of this entity.
- Understanding of the early bony changes might lead to early diagnosis and eventually to more targeted therapy.
- Much needed future research paths are suggested.

Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic, relatively common condition, with an average prevalence of approximately 10% in people >50 years of age. Despite its old characterisation (previously described as 'ankylosing hyperostosis' by Forestier and Rotes-Querol),[1] DISH is still insufficiently investigated and understood. The disease is characterised by continuous ossification of ligaments and entheses, especially in the axial skeleton but also in peripheral joints. Classification of DISH is being made when large bridging osteophytes occur in at least four adjacent thoracic vertebrae, as detected by conventional radiographs.[2] Indeed, the disease usually affects the thoracic spine, without further explanation for this preference in location but other spinal segments or peripheral joints might also be affected. In contrast to the impressive structural changes, patients with DISH may be largely asymptomatic. This is also one of the reasons why this condition has not received as much attention from both clinicians and researchers due to its difficulty for early diagnosis and appropriate treatment. Nevertheless, the role of DISH as a condition associated with many systemic conditions such as underlying metabolic derangements or cardiovascular disease has been confirmed in clinical studies in the last decades.[3–8] However, it remains to be established if, and to what extent, DISH is an independent cardiovascular risk factor.

At present, imaging is the most commonly used method to consider DISH as a diagnosis.

On the other hand, CT has been shown to be more sensitive in the assessment of structural changes in DISH, as compared with conventional radiographs.[9] Entheseal ossification and calcifications may falsely increase bone mineral density readings by dual-energy X-ray absorptiometry, but peripheral quantitative CT has shown that bone density and geometry are not altered in patients with DISH.[10] Nevertheless, CT examinations are generally rarely performed even in suspicious cases due to the associated radiation exposure. Recently, a few studies with MRI or ultrasonography (US) suggested that a local entheseal inflammatory process might precede the ossification process.[11 12] Therefore, more studies are needed to reiterate these findings and explore their correlation with biopsy findings.

Based on this background, a group of investigators met in Tel Aviv, Israel, on 22–23 May 2016. The goals of the meeting were to discuss the present published evidence on DISH, identify possible unmet needs and discuss

how to overcome these based on future collaborative research. The group was composed of rheumatologists, radiologists, geneticists and an orthopaedic surgeon. Presentations and discussions were conducted based on a literature review and an update of the current knowledge on clinical manifestations, implications on the diagnosis and complications during the course of the disease. The use of basic and more advanced imaging techniques for investigating the pathogenesis and differentiation of DISH from other diagnoses with similar imaging findings were also discussed. The discussion concluded with the current update on data from genetic evaluations as well as a discussion on their impact on future interventions.

CLINICAL MANIFESTATIONS

The term DISH has been coined 1975 when Resnick realised that the disease is not limited to the spine but rather involves also the appendicular skeleton. However, still the clinical manifestations of the axial skeleton remain elusive with a very limited number of controlled studies. While there is evidence for perceived spinal stiffness, the question of whether spinal DISH is a painful condition in general and whether musculoskeletal pain occurs due to inflammatory or chronic hyperproliferative changes remains unanswered.[13–17]

For the spinal manifestations, it has been further shown that in end-stage DISH subjects, due to the inability of the stiff spine to absorb tearing forces, the vertebral column becomes more vulnerable to trauma which leads to fractures even after relatively low-energy trauma.[18–20] Therefore, the group unequivocally confirmed that due to the pathologically increased new bone formation, particular attention needs to be drown to the research of the disease-related biomechanical changes. In addition, involvement of the cervical spine and proliferative bone changes in its anterior part can lead to mechanical airway obstruction, difficulties with swelling and may also complicate medical procedures that require access to the upper airways and the digestive systems.[21] Finally, involvement of other parts of skeleton such as involvement of the sternocostal and costochondral junctions may also result in restrictive lung disease due to limited expansion of the thoracic cage.

There have been several reports that described peripheral joints manifestations especially in the form of hypertrophic osteoarthritis (OA), osteoarthritis involving joints usually not affected by OA such as the elbow and shoulder, and enthesopathies related to joints (ie, tibial tuberosity, elbow) and in sites unrelated to joints (ie, plantar fascia, iliolumbar ligament).[22–29]

While many studies describe the radiographic findings of the axial and appendicular manifestations of DISH, there are very few controlled studies that have tried to evaluate the prevalence and quality of the overall clinical manifestations. Apart from the obvious stiffness of the axial skeleton and the peripheral joints, it is not clear whether pain and swelling are always present in the involved joints. A single study reported the association of soft tissue tenderness with DISH and its impact on quality of life, measured by the Short Health Assessment Questionnaire.[30] Other studies addressed the role of entheseal involvement and their predictive value of being diagnosed with DISH. Only two radiographic studies showed that some patients with pelvic enthesopathy had an increased predictive value in diagnosing DISH.[31 32] Hyperostotic spurs at the olecranon, lateral and medial epicondyle had the highest prevalence and disclosed the most pronounced discrimination for elbow DISH. Mechanical factors such as physical activities and handedness, and sex influenced the formation of these spurs.[33] In conclusion, the group members felt that more reliable data is needed in order to consider the role of the appendicular skeleton involvement in future classification criteria. Finally, a few controlled studies reported on various metabolic and constitutional derangements in DISH such as obesity, arterial hypertension, diabetes mellitus, hyperlipidaemia and metabolic syndrome. These facts were not supported by all investigators, and causal relationship has not been definitively established so far. However, this association could also be a potential field for further investigation.

IMAGING CHARACTERISTICS

The defining imaging characteristics of DISH are the flowing osteophytes mainly in the thoracic spine. The coarse and thick bony spinal bridges form along the anterior longitudinal ligament in a more horizontal orientation and mainly on the right side. These features help distinguish DISH from ankylosing spondylitis (AS), in which thin, delicate vertically oriented syndesmophytes are the hallmark. The differences between DISH and AS are not limited to the radiographic appearance. In fact, patients with DISH may have some clinical features similar to those observed in AS. However, they are usually older than the patients with AS and have associated metabolic derangements.[34 35] Even with modern imaging (ie, MRI), the addition of clinical parameters improve the ability to distinguish between DISH and AS.[36] Enthesopathy is another prominent feature in DISH, and crude entheseal calcification is a common finding in the pelvis as well as more peripheral joints such as the hands, ankles and feet.

It is possible to diagnose spinal involvement in DISH on plain radiographs, but due to its three-dimensional visualisation, CT offers a more detailed evaluation of the bone formation process.[37–39] These modalities are also helpful in the evaluation of peripheral enthesopathy for which US is also a readily available and sensitive tool.[40]

A small case–control study suggested that MRI was capable to detect vertebral corner fat infiltration similar to findings in AS. The significance of this finding in relation to potential shared pathogenesis needs to be further evaluated.[36]

The commonly accepted Resnick and Niwayama classification criteria for spine require flowing osteophytes

over four vertebral bodies and in addition the preservation of the intervertebral disc space without apparent degenerative disc disease as well as absence of apophyseal or sacroiliac joints' erosions, sclerosis or ankylosis.[2] However, enthesopathy in the sacroiliac joints exists as anterior bony bridges and intra-articular bridges mimicking the joint ankylosis of AS.[41]

The Resnick and Niwayama criteria target DISH in its end stage in which research as well as intervention is of little potential use. In an attempt for earlier identification of DISH, Utsinger in his criteria lowered the threshold of flowing osteophytes to only three contiguous vertebral bodies but added the presence of peripheral enthesopathies.[42] New classification criteria integrating the accumulated knowledge on DISH from recent years, may help in detecting DISH in its earlier stage, facilitating research into its pathogenesis.

PATHOGENESIS OF DISH

The current knowledge on the pathogenesis of DISH is very limited. Some of the pathogenic pathways have been adopted from analogous entities such as ossification of the posterior longitudinal ligament (OPLL). The main concept is based on the excess of growth factors that might induce transformation of mesenchymal cells into fibroblasts and osteoblasts such as insulin, insulin-like growth factor 1, transforming growth factor-β1, platelet-derived growth factor-BB, prostaglandin I2 and endothelin 1.[6 43–47] On the other hand, reduced activity of inhibitors of bone-promoting peptides such as matrix Gla protein, bone morphogenic protein-2 inhibition or Dickkopf-1 (Wnt–β-catenin pathway inhibition) have also been considered.[48–58] Previous examination of spinal entheses from cadavers showed findings similar to those observed on CT scans and concluded that the intervertebral disc degeneration has a limited role in the pathogenesis of DISH.[59] It has been reported that some animal breeds (ie, Boxer) have a high prevalence of DISH,[60] suggesting a genetic basis for this condition. A recently developed mouse model might be useful in future studies on DISH.[61]

There have been a few case descriptions of familial cases of DISH.[62 63] A single study reported that collagen type I alpha1 and vitamin D receptor polymorphisms do not seem to contribute to DISH aetiology. Other studies have looked into genetics of OPLL which has been extensively studied and reported several genetic associations mainly in Japanese patients. DISH and OPLL can coexist and have some common features such as the ligamentous ossification. One of the genes reported to be associated with OPLL, COL6A1, has been studied in patients with DISH. The association of this gene with DISH was maintained for Japanese patients without OPLL but not for Czech patients.[64 65] A very recent study, examined one of the OPLL genome-wide association study loci and identified encoding R-spondin 2 (RSPO2) as a susceptibility gene for OPLL.[66] It is therefore important to study the genetics of DISH in populations with low prevalence of OPLL in order to isolate the genetic impact. It has been suggested to perform sib-pair linkage studies, case–control studies and later a genome-wide studies.

THERAPEUTIC CONSIDERATIONS

The review of the literature showed that there are no studies dealing with the treatment of patients being diagnosed particularly with DISH. In daily practice, the treatment approach is based on the knowledge gathered mainly from the treatment guidelines for other conditions or from empirical approaches of single patients. In fact, the treatment of pain in the spine, in peripheral joints or entheses is largely based on the practice used for the treatment of osteoarthritis with analgesics, local or systemic non-steroidal anti-inflammatory drugs (NSAIDs), random physiotherapeutic modalities and lifestyle changes such as diet programmes. Patients employed with heavy manual labour, can benefit from ergonomic, occupational therapy and aptitude counselling.[33] Due to the comorbidities that often accompany DISH, it has been suggested to avoid medications that might enhance insulin secretion such as sulfonylureas, β-adrenergic blockers or thiazide diuretics.[67]

Due to the propensity of patients with DISH to develop heterotopic ossification following joint replacement surgeries, it has been suggested to adopt preventive measures such as the use of NSAIDs and/or irradiation in the perioperative period.[68–70] However, the prevention or inhibition of soft tissue ossification has not been investigated systematically in patients with DISH. Therapeutic studies in DISH are hampered by several reasons. The most important is that the present classification criteria only allow for recognition of DISH in a late stage of a well-established condition. Furthermore, it has recently been shown that the time elapsed from the initial ossification process to a full completion of the ossified bridges may last up to approximately 10 years.[71] Therefore, even in the cases of early diagnosis, a possible effect of early treatment on the ossification process will need an observation of the treatment intervention for at least a decade. At present, there is only indirect evidence for possible therapeutic interventions. Besides the already mentioned interventions with NSAID treatment, which may prevent heterotopic ossifications, it has been suggested that bisphosphonates may be able to reduce osteophyte formation in both animal models and humans, which suffices them as candidate options. If DISH would be confirmed as a local inflammatory process, various anti-inflammatory agents, including biological agents, could prove to be potentially useful. However, such treatment has not been tried out in patients with DISH so far, and due to its economic burden, this hypothesis needs to be meticulously investigated. Finally, since trauma to the ankylosed spine may lead to spinal fractures with complications and death, or, complications during upper gastrointestinal/airway

procedures, this also needs to be taken into account by physicians treating these patients.[72]

PROPOSED FUTURE STEPS

There was a general group agreement that the research of DISH is currently hampered by the present classification criteria that allow to identify the main diagnostic features of the condition late in its course. It is therefore mandatory to identify patients in the early phases of the disease. It was suggested, that patients with metabolic syndrome and/or increased deep subcutaneous abdominal adipose tissue can be good candidates for this purpose. MRI was considered the preferred imaging modality to detect early changes in the axial and peripheral skeleton, due to its ability to detect early inflammatory changes around and within the bone. In addition, biopsies from such lesions could be one way to detect factors that might affect the mesenchymal cells differentiation into bone-forming cells and to identify bone-remodelling markers.

Due to all the reasons described above, the group felt that the current classification criteria for identification of DISH need to undergo revision, including the spinal involvement of the patients and considering incorporation of metabolic, constitutional and clinical parameters into a new set of classification criteria. From the criteria available at present, an interim solution to improve sensitivity and specificity in daily practice could be the choice to use the Utsinger classification criteria,[14] which allow classifying DISH with a greatly reduced number of spinal bridges but with contemporary involvement of peripheral entheses.

In summary, a first organised attempt to systematically collect and review the current evidence of DISH was conducted by a group of experts or persons with special interest in this field. The group concluded that, despite the long efforts so far, still little is known about DISH and its spinal and extraspinal manifestations, its pathogenesis, the genetic basis and the therapeutic approach for patients diagnosed with this condition. Furthermore, the current classification criteria allow to classify the disease only in its late stage, where any preventative measures are not able to influence the further deterioration. A research agenda was proposed with the aim to improve the knowledge about all aspects of the disease and be able to propose a classification that can be applied in daily practice and improve the course, the comorbidities and sequela of this chronic disease.

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The fourth author of this article should be cited as Bruges Armas J (and not Jacome BA).

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