Coined in 1975 by Resnick et al., diffuse idiopathic skeletal hyperostosis describes a systemic condition that is mainly characterized by flowing ossification of the spine and, less frequently, peripheral entheses. Its overall incidence is 6-12%, but it is more frequently observed in males than in females and subjects aged >50 years, and its increased prevalence in people aged >70 years suggests that the course of the disease begins between the third and fifth decade of life but its clinical manifestations do not appear until later. Its pathogenesis and etiology remain unknown, but it has been reported to be associated with a number of genetic, metabolic, and constitutional factors.

The aim of this review is to describe the main features of the disease and stimulate research into its pathogenesis, prevention, and treatment.
obesity, a high waist circumference ratio, dyslipidemia, high levels of growth-promoting peptides, hyperuricemia, and the use of retinoids. Consequently, patients with DISH are more likely to be affected by metabolic syndrome and are at higher risk of developing coronary artery disease. It has been shown that they are subject to a higher incidence of coronary events than non-DISH patients and, as the increased risk is greater than that calculated on the basis of traditional risk factors, DISH may even be an independent risk factor for ischemic heart disease. An association between DISH and type 2 DM has been reported in most (but not all) studies, and HLA B8 is common to both conditions.

The target organs in DISH are the entheses, which consist of fibroblasts, chondrocytes, collagen fibers and a calcified matrix. The differentiation of ligament mesenchymal cells into chondrocytes and subsequent endochondral ossification is promoted by insulin and insulin-like growth factor-1, and may therefore contribute to the ossification process. Other bone-forming promoting peptides such as bone morphogenetic protein(BMP)-2, and growth hormone (GH) can also stimulate the differentiation of mesenchymal stem cells into fibroblasts and chondroblasts, and induce alkaline phosphatase activity and collagen synthesis. It is worth noting that GH levels may be higher in synovial fluid and erythrocytes than in serum, thus suggesting that blood supply may play a role. The activation of environmental factors such as platelet-derived growth factor (PDGF)-BB and transforming growth factor (TGF)-β1 in ligament cells stimulates the activation of NF-κB, which affects the osteoblastic differentiation of mesenchymal cells. Other cytokines such as PGI₂, and endothelin-1 may also induce osteogenic differentiation in spinal ligament cells by means of various mechanisms.

The predilection of the ossifying process for the right side of the thoracic spine is probably due to the pulsation of the aorta, which interfere with the production of osteophytes. This theory is supported by the findings of studies of patients with situs inversus in whom the ossifying process takes place on the left side of the thoracic spine.

The formation of new bone in DISH patients has some similarities with the process observed in patients with spondyloarthritis, which suggests that it may also be preceded by local inflammation.

**Clinical manifestations**

The clinical manifestations of DISH have not been clearly established: for example, it is not known why the condition is painless in some patients but painful in others. The level of pain and disability is significantly higher than in healthy subjects, but similar to that observed in patients with spondylitis. It is generally accepted that spinal involvement in DISH is accompanied by stiffness that may also involve the cervical and lumbar spine, and nearly

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**Table 2. Diffuse idiopathic skeletal hyperostosis diagnostic criteria.**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Resnick and Niwayama criteria</th>
<th>Utsinger criteria</th>
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<tr>
<td>Radiographic findings of flowing anterior ossification of at least four consecutive vertebrae in the thoracic spine</td>
<td>Continuous ossification along the anterolateral aspect of at least four contiguous vertebral bodies, primarily in the thoracolumbar spine. Ossification begins as a fine ribbon-like wave of bone but commonly develops into a broad, bumpy, buttress-like band of bone.</td>
<td></td>
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<tr>
<td>Preservation of intervertebral disc space at involved level</td>
<td>Continuous ossification along the anterolateral aspect of at least two contiguous vertebral bodies.</td>
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<tr>
<td>Absence of apophyseal joint bony ankylosis and sacroiliac joint erosion, sclerosis, or intra-articular osseous fusion</td>
<td>Symmetrical and peripheral enthesopathy involving the posterior heel, superior patella or olecranon, with the enthesal new bone having a well-defined cortical margin.</td>
<td></td>
</tr>
</tbody>
</table>

| Exclusions criteria: | |
| - abnormal disc space height in the involved areas | |
| - apophyseal joint ankylosis | |

50% of DISH patients show a reduced range of motion.\textsuperscript{39,40} New vertebral body and facet joint bone formation in the lumbar spine is not uniformly one-sided\textsuperscript{41} and, in addition to restricting movement, may also induce spinal stenosis and neurological manifestations.\textsuperscript{42} It has been reported that similar cervical spine involvement is associated with complications such as: dysphagia, stridor, hoarseness, aspiration pneumonia, sleep apnea, and atlanto-axial disease.\textsuperscript{43}

However, unlike spondylosis (which affects the mobile lower cervical and lumbar spine) it should be borne in mind that DISH has a predilection for the thoracic spine and, although it is considered to be a non-inflammatory condition, some patients adopt the posture that is typical of patients with ankylosing spondylitis.\textsuperscript{44,45} The two entities are usually differentiated on the basis of age at the time of presentation, clinical manifestations, the association with HLA B27 and imaging findings (Table 1).

The involvement of peripheral joints has been reported with various frequency. This involvement includes lesions to the large entheses, which may occur in proximity to the joints (e.g. joint capsules or peri-articular ligaments and tendons) or distant from the joints (e.g. tibial tuberosity, Achilles enthesopathy). Other expressions of peripheral joint involvement include: hypertrophic bone changes, the involvement of joints not usually affected by osteoarthritis, reduced range of motion, and pain.\textsuperscript{46-48}

Osteoarthritis may accompany DISH because of the similar age groups affected by the two conditions, which may share similar pathogenetic mechanisms such as a movement-restricting thickening of the collateral ligaments of the peripheral joints, increased intra-articular pressure, and subsequent damage. This may explain the involvement of atypical joints not usually affected by osteoarthritis as well as the hypertrophic osteoarthritic observed in the commonly affected joints.

\textbf{Diagnosis}

The diagnosis of DISH is based on the presence of large bridging osteophytes involving at least four contiguous vertebrae in the thoracic spine or ossification of the anterior longitudinal ligament, preserved intervertebral disc space, and the absence of inflammation of the facet or sacro-iliac joints (Table 2).\textsuperscript{49} A number of variations of the criteria classification exist, but none of them has been validated. For example, the criteria suggested by Utsinger include peripheral enthesopathies, and a probable diagnosis of DISH can be made even if there are fewer vertebral bodies involved, provided that they are accompanied by bilateral, well-corticated enthesopathies of the heel, olecranon, and patella. It has also been suggested that peripheral enthesopathies may indicate an early stage of DISH that may evolve over time until it takes on its full radiological characteristics.
logical appearance (Table 2). Musculoskeletal Ultrasoundography could be useful in this stage as it is able to identify both inflammatory and chronic changes in enthesis and could be used for long term follow-up as it can be easily repeated over time and provide useful information in the evolution of the disease (Figure 1). However, it must be stressed that experts in the field believe that there is still insufficient evidence to include peripheral involvement in the classification criteria.

Laboratory measurements of the erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and antinuclear antibodies are often normal.

A diagnosis of DISH requires clear radiographic evidence of new bone formation, and this precludes the detection of early events such as any preceding inflammation. However, magnetic resonance imaging (MRI) of the spine in patients with DISH has revealed the early involvement of vertebral corners, similar to those detected in spondyloarthritis and the similarity of DISH to inflammatory spinal disease is also supported by the similar rate of new bone formation (Figures 2-5).

**Treatment**

No controlled trial of DISH treatment has yet been conducted, and most of the treatments used have been extrapolated from osteoarthritis treatments. In the presence of pain, analgesics or NSAIDS may be useful, and the same is true of topical corticosteroid administration or corticosteroid injections in peripheral sites.

As many patients with DISH also have atherosclerotic diseases, it seems appropriate to treat metabolic disorders such as obesity, hyperlipidemia, hypertension, and DM. Although it has not been scientifically tested, an effort should be made to avoid treatments known to increase insulin levels such as beta blockers and thiazide diuretics.
Given the propensity for new bone formation in DISH patients, those undergoing joint replacement surgery should be administered treatment aimed at preventing heterotropic ossifications. Caution is advised when carrying out an upper endoscopic examination or intubation in patients with cervical spine involvement. Finally, spinal stiffness in patients with DISH means that they are susceptible to spinal fractures, sometimes with severe neurological damage; it is therefore recommended to take measures aimed at preventing falls.

References


