Diffuse idiopathic skeletal hyperostosis: a review

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Abstract

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.

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Key words: Diffuse idiopathic skeletal hyperostosis; metabolic syndrome; clinical manifestations; radiographic features.

Contributions: all authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interests.

Availability of data and materials: not required.

Ethics approval: not required.

Received for publication: 1 December 2020.
Accepted for publication: 3 December 2020.

Licensee PAGEPress, Italy
Beyond Rheumatology 2020; 3:52
doi:10.4081/br.2020.52

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a hypertrophic bone disease whose main characteristic is new bone formation, which mainly affects the spine but may also involve peripheral sites, usually the entheses. Its clinical manifestations have not been fully explored, and researchers still disagree on its spinal and peripheral expressions. There are a number of classification criteria, but those described by Resnick are the most widely accepted and used. The pathogenetic mechanisms leading to new bone formation are not fully understood, but suggestions range from metabolic to inflammatory causes. The disease has been well known since antiquity and is relatively common in certain age groups; however, it is not recognized by many clinicians and has not been sufficiently investigated.

Epidemiology

DISH has been found in human remains dating back 4000 years and between 500 and 700 A.D., when its estimated prevalence was only 3.7%, probably because of the younger age of the deceased.[1,2]

Only a few modern epidemiological studies of DISH have been published, but it is known that it is more frequent among men than among women (a male:female ratio of approximately 2:1), and that its prevalence increases with age and depends on the clinical setting, geographical location, and ethnicity. Its prevalence in population-based studies has been reported to be slightly more than 10% in patients aged >70 years,[3] although it is higher among patients attending medical facilities, and may be as high as 35% in the older male population;[4,5] DISH has also been found in 28% of autopsied spines.[6] Its prevalence is even higher among Jews living in Jerusalem (reaching 46% in the case of men aged >80 years),[7] but much lower among older Asians (9%) and Africans (13.6%).[8,9]

Etiology and pathogenesis

The cause and pathogenesis of DISH are still unclear, although it has been reported to be associated with a number of genetic, metabolic, and constitutional factors, as well as with various bone formation–promoting peptides, all of which may contribute to the condition.

Although it has not yet been demonstrated in humans, the existence of familial clusters of DISH and families characterized by the early presentation of the disease suggests that genetic factors may play a role in its pathogenesis.[10,11]

The most frequent pathogenetic pathways associated with DISH are metabolic and constitutional disorders, such as hypertension, type 2 diabetes mellitus (DM), hyperinsulinemia,

obesity, a high waist circumference ratio, dyslipidemia, high levels of growth-promoting peptides, hyperuricemia, and the use of retinoids.[12-20] Consequently, patients with DISH are more likely to be affected by metabolic syndrome and are at higher risk of developing coronary artery disease.[21] 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.[22] An association between DISH and type 2 DM has been reported in most (but not all) studies,[5,17,20,23,24] and HLAB8 is common to both conditions.[25]

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.[26-29] 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.[2] It is worth noting that GH levels may be higher in synovial fluid and erythrocytes than in serum,[30-32] 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 PGI_2, and endothelin-1 may also induce osteogenic differentiation in spinal ligament cells by means of various mechanisms.[32]

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.[25,33]

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.[34,35]

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.[36,37] The level of pain and disability is significantly higher than in healthy subjects, but similar to that observed in patients with spondylosis.[38] It is generally accepted that spinal involvement in DISH is accompanied by stiffness that may also involve the cervical and lumbar spine, and nearly

Table 1. Main features distinguishing DISH and axial spondylitis (AS).

Features	AS	DISH
Sacro-iliac (SI) joint erosions	X	
Apophyseal joint obliteration	X	
Frequent ossification of the anterior longitudinal ligament		X
Enthesopathies with erosions	X	
Mild or even painless disease		X
HLA B27	X	
Incidental discovery		X
Older age at time of presentation		X

Table 2. Diffuse idiopathic skeletal hyperostosis diagnostic criteria.

Resnick and Niwayama criteria
Radiographic findings of flowing anterior ossification of at least four consecutive vertebrae in the thoracic spine or ossification of the anterior longitudinal ligament
Preservation of intervertebral disc space at involved level
Absence of apophyseal joint bony ankylosis and sacroiliac joint erosion, sclerosis, or intra-articular osseous fusion
Utsinger criteria
Definite DISH 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
Probable DISH Continuous ossification along the anterolateral aspect of at least two contiguous vertebral bodies
Probable DISH Symmetrical and peripheral enthesopathy involving the posterior heel, superior patella or olecranon, with the entheseal new bone having a well-defined cortical margin
Exclusions criteria: - abnormal disc space height in the involved areas - apophyseal joint ankylosis

DISH, diffuse idiopathic skeletal hyperostosis. Data from Resnick and Niwayama, 1976[40] and Utsinger, 1985.[39]

50% of DISH patients show a reduced range of motion.[39,40] New vertebral body and facet joint bone formation in the lumbar spine is not uniformly one-sided[41] and, in addition to restricting movement, may also induce spinal stenosis and neurological manifestations.[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.[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.[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.[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.

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).[49] A number of variations of in 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 radio-

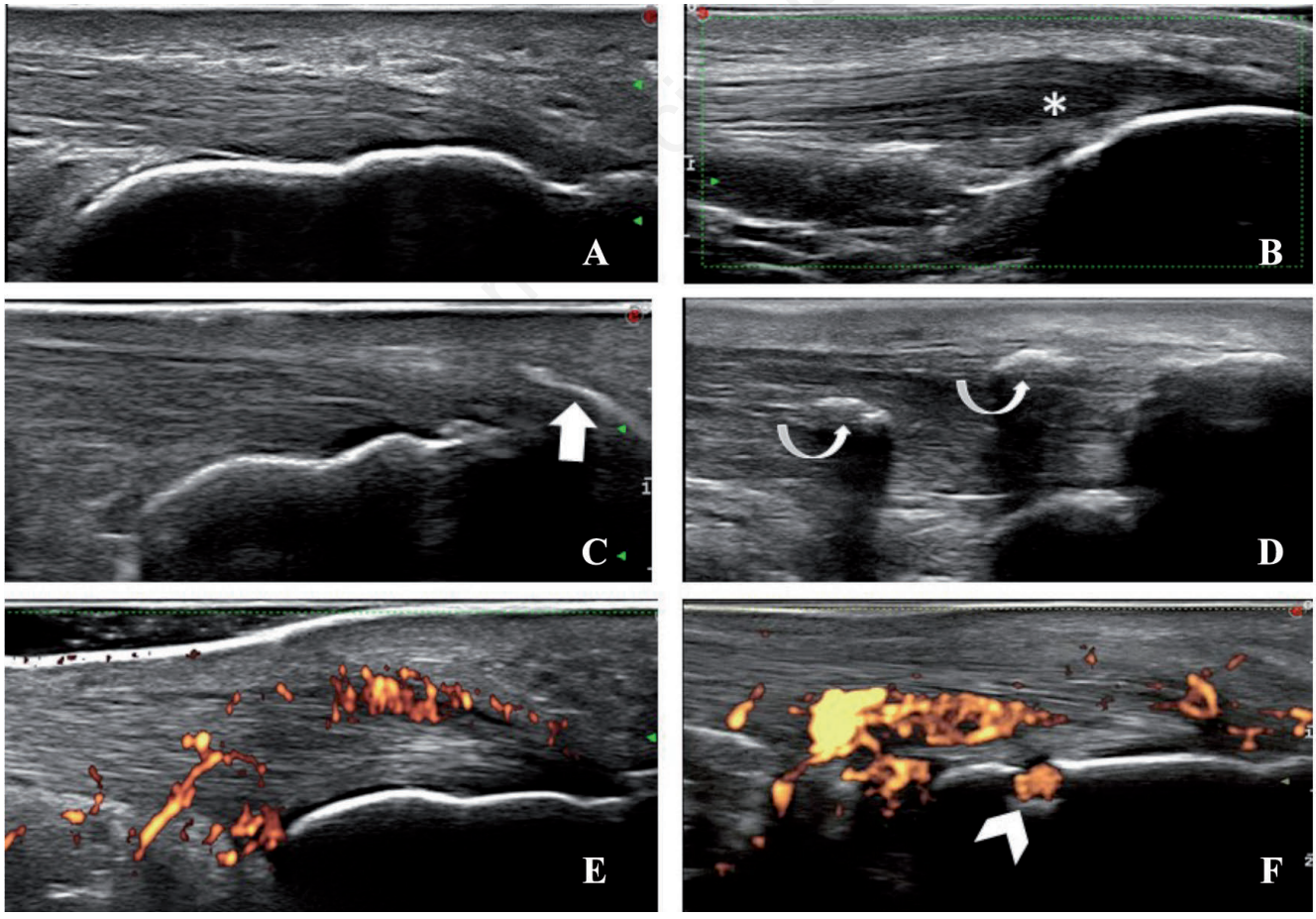

Figure 1. Ultrasound features of grey scale and power Doppler changes in enthesis. A) normal tendon enthesis (Achilles tendon); B) thickening and hypoechogenicity of the tendon insertion (asterisk); C) enthesophyte (arrow); D) tendon calcifications (curved arrows); E) power Doppler signal in the insertional tract of the tendon; F) power Doppler signal and erosions of calcaneal profile (typical aspect of enthesitis in spondyloarthritis).

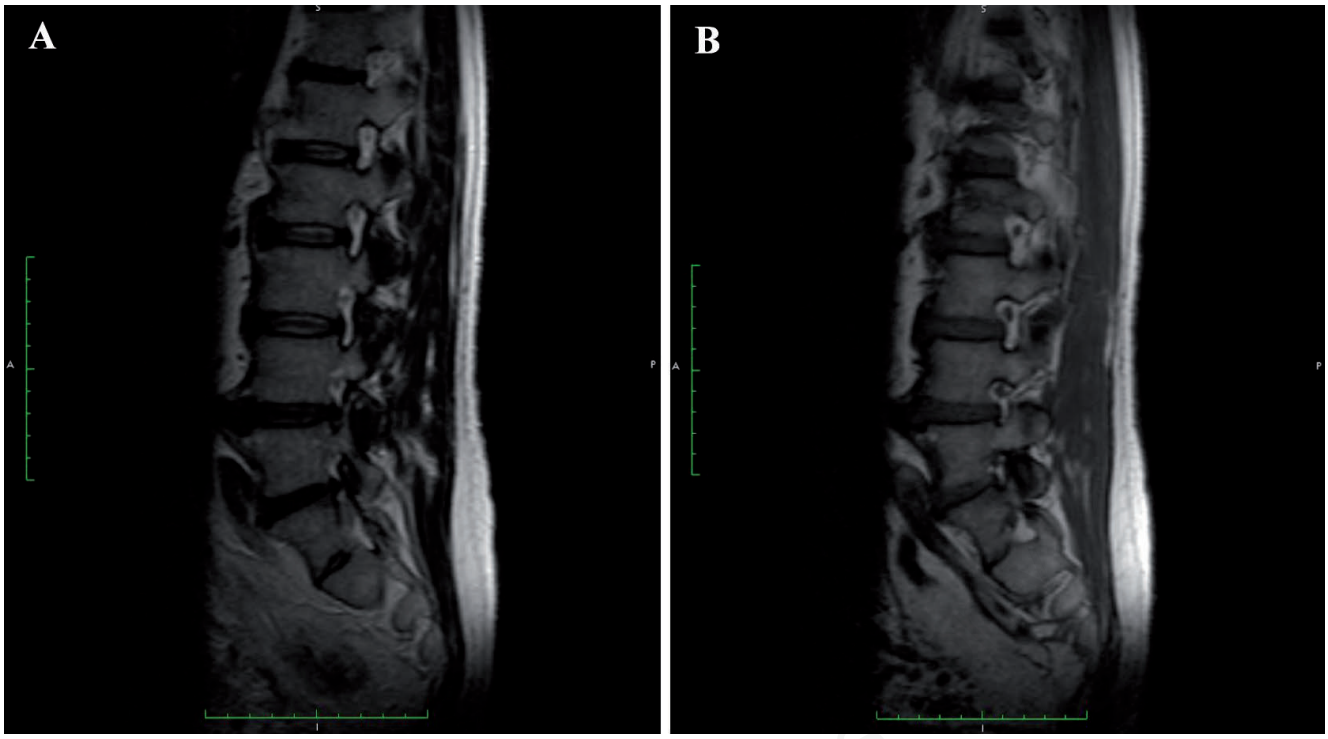

Figure 2. The sagittal T2 weighted image (A) and the sagittal T1 weighted (B) image show ossification of the anterior longitudinal ligament over four vertebral bodies with osteophytes at L4-L5. Anterior corner fat deposition lesions can also be observed at L1-L2 and L4-L5.

logical appearance (Table 2).[50] Muscoloskeletal Ultrasonography could be useful in this stage as it is able to identify both inflammatory and chronic changes in enthesis[47] 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.[51]

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,[34] and the similarity of DISH to inflammatory spinal disease is also supported by the similar rate of new bone formation[35] (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,[52] 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.

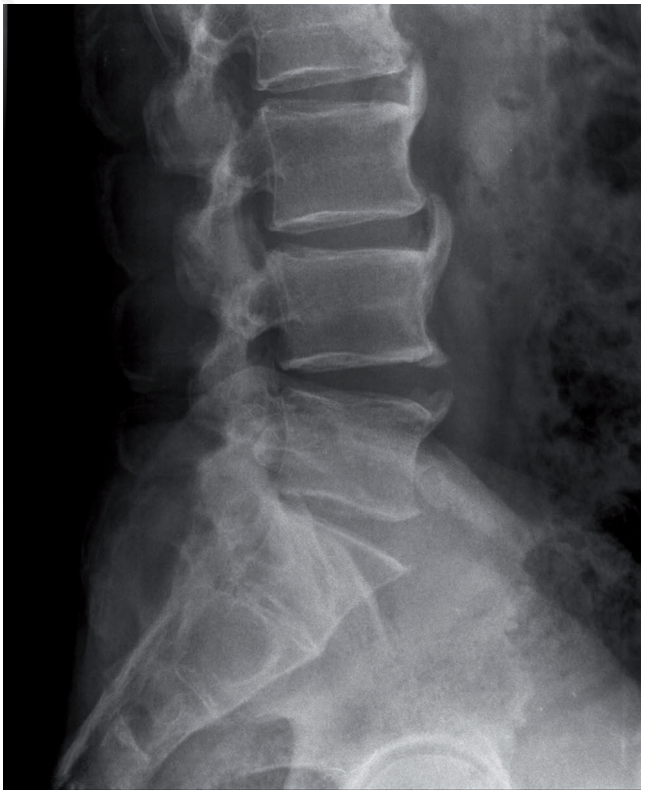

Figure 3. Lateral view of the lumbar spine reveals bony spinal bridges anterior to the vertebral bodies and discs.

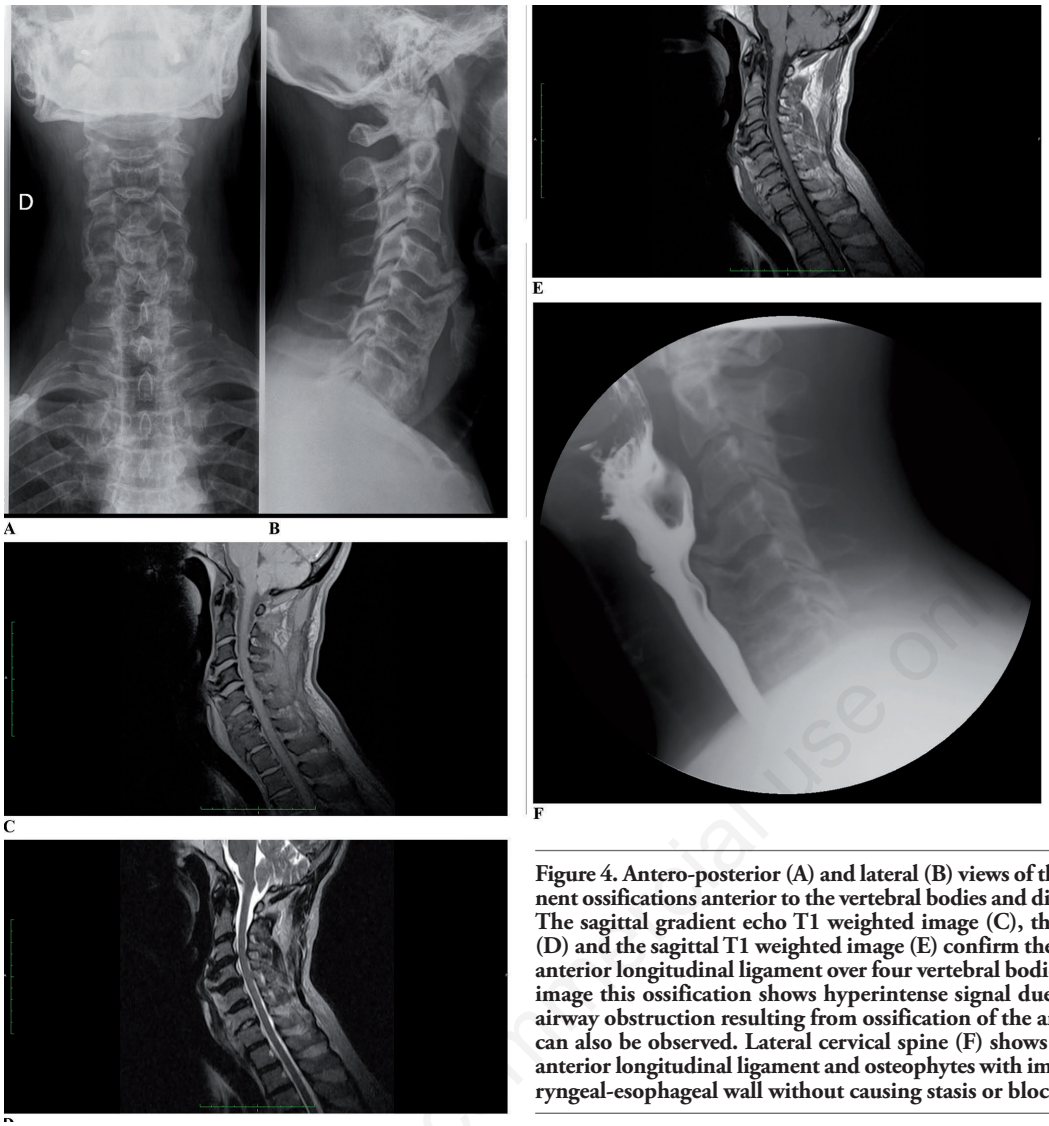

Figure 4. Antero-posterior (A) and lateral (B) views of the cervical spine reveal prominent ossifications anterior to the vertebral bodies and discs and osteophytes at C3/C7. The sagittal gradient echo T1 weighted image (C), the sagittal T2 weighted image (D) and the sagittal T1 weighted image (E) confirm the exuberant ossification of the anterior longitudinal ligament over four vertebral bodies. In the sagittal T1 weighted image this ossification shows hyperintense signal due to fat deposition. Moderate airway obstruction resulting from ossification of the anterior longitudinal ligament can also be observed. Lateral cervical spine (F) shows exuberant ossification of the anterior longitudinal ligament and osteophytes with impinging on the posterior pharyngeal-esophageal wall without causing stasis or blockage of the contrast medium.

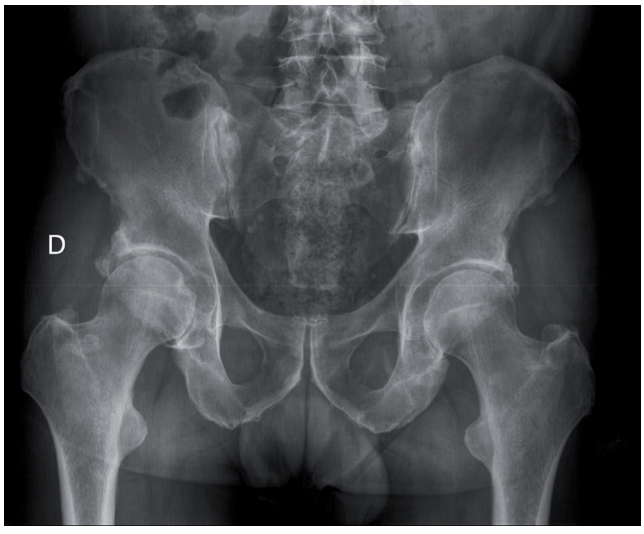

Figure 5. The anteroposterior pelvic X-ray shows hyperostosis around the bilateral hip joints, which would predispore to *pincer* type femuro-acetabular impingement.

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.

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