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Diffuse idiopathic skeletal hyperostosis, beyond the musculoskeletal system

Fabiola Atzeni[1*], Alessandra Alciati[2,3], Shay Brikman[4], Reuven Mader[4]

[1]Rheumatology Unit, Department of Experimental and Internal Medicine, University of Messina, 98125 Messina, Italy
[2]Department of Clinical Neurosciences, Hermanas Hospitalarias, Villa S. Benedetto Menni Hospital, 22032 Albese con Cassano, Como, Italy
[3]Humanitas Clinical and Research Center-Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Rozzano, 20089 Milan, Italy
[4]Rheumatic Diseases Unit, Ha'Emek Medical Center, Afula 18101, Israel

***Correspondence:** Fabiola Atzeni, Rheumatology Unit, Department of Experimental and Internal Medicine, University of Messina, 98125 Messina, Italy. atzenifabiola@hotmail.com
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Abstract

It has been suggested that diffuse idiopathic skeletal hyperostosis (DISH), a skeletal disease characterized by the ligamentous ossification of the anterolateral spine, is a radiological entity with no clinical implications; however, many patients suffer from chronic back pain, decreased spinal mobility, and postural abnormalities. Additionally, the pathological new bone formation at the cervical and thoracic levels may mainly produce dysphagia and breathing disturbances. Over the last 20 years, a close association between DISH, obesity, diabetes mellitus (DM), and metabolic syndrome (MS) has emerged. However, a causal relationship has not yet been established. It has been suggested that the longer life expectancy and the growing incidence of MS in Western populations, associated with the tendency of DISH to manifest in later life, may increase the DISH prevalence rates in the following decades. Future investigations should focus on the early DISH phase to clarify pathogenetic mechanisms and identify targeted therapies.

Keywords

Diffuse idiopathic skeletal hyperostosis, cardiovascular disease, diagnostic criteria, extra-spinal involvement, metabolic syndrome

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a skeletal disease of unknown etiology characterized by ligamentous ossification of the anterolateral spine that Forestier and Rotes-Querol first described more than 50 years ago [1]. The main targets of the disease process are entheses, which are subsequently thickened, calcified and/or ossified. It has also been suggested that DISH may be just a radiological entity, but many patients manifest significant clinical symptoms, complications, and comorbidities.

DISH is often classified as a form of osteoarthritis (OA). However, although it often co-exists with OA, the two conditions differ in terms of prevalence in the general population, gender distribution, the primarily involved anatomical site, and the type of involvement and distribution in the spine and peripheral joints [2, 3]; DISH is, therefore, a distinct clinical entity [3]. Although the disease may be asymptomatic, some patients experience chronic back pain [4–7], decreased spinal mobility, and postural abnormalities that resemble those associated with long-standing advanced ankylosing spondylitis [8–10]. Furthermore, the sites of ossification and the subsequent production of large osteophytes may cause severe clinical manifestations that include dysphagia [6], quadriplegia [7], esophageal obstruction [3], dyspnea and hoarseness [11], atlanto-axial subluxation [12] and others, especially when the cervical spine is affected.

Validated diagnostic criteria are not yet available. However, four classification criteria can be described. One of them is the Resnick and Niwayama's [13] classification, requiring the involvement of at least four contiguous thoracic vertebrae with preserved intervertebral disc space, and the absence of inflammatory changes to the apophyseal or sacroiliac joints. The Arlet and Mazières's [14] classification defines its sufficient requirements for a diagnosis of DISH as the involvement of three contiguous vertebral bodies at a lower thoracic level. Julkunen et al.'s [15] requirement is the presence of flowing anterolateral osteophytes that connect two vertebral bodies in at least two thoracic spine sections.

The peripatellar ligaments, Achilles tendon insertion, plantar fascia, and olecranon might also be affected [6] despite being ignored by all three classifications above.

The fourth classification is that of Utsinger [16], who added the presence of peripheral enthesopathies to the diagnostic measures and defined three categories: A (definite DISH), B (probable DISH), and C (possible DISH). However, these criteria are limited because other peripheral sites may be involved, such as the metacarpophalangeal joints, shoulders, ribs, and pelvis [17]; furthermore, peripheral joint involvement is often associated with hypertrophic changes, enthesopathies, and entheseal calcifications and ossifications in other sites.

Some authors have described patients with DISH in the thoracic region as suffering from displaced spinal fractures with neurological deficits after minor trauma, such as a fall from a standing position or a low-speed car collision [18, 19]. Extraspinal manifestations of DISH have also been described. For instance, the ossification of tendons and insertions reducing both active and passive joint mobility [3], reduced chest expansion [20], and bone proliferations [21]. This supports the idea of inadequacy of the currently available criteria, with the potential of making diagnostic mistakes [22].

The reported prevalence of DISH varies widely, probably because of differences in the studied populations. The only general population-based study found a prevalence of 3.8% in males and 2.6% in females, but these percentages rose to 10.1% and 6.7% in subjects aged 70 years or more [15]; however, it has also been reported to be 2.9% in Korea and up to 25% in the USA [23, 24]. DISH is more common in people aged over 50, among whom its prevalence in the USA is 25% in men and 15% in females, rising to 35% and 26% in those aged over 70 [24].

The causative factors are not known yet, although the attention has been drawn to various genetic, metabolic, endocrine, and environmental factors [25, 26]. These two studies have been focused on the genetic factors associated with DISH and ossification of the posterior longitudinal ligament (OPLL), a condition often associated with DISH. Complex genetic analyses conducted to discover common genetic variants contributing to the risk of developing DISH have identified several genes involved in bone remodeling, supporting the hypothesis that overactive osteogenesis is involved in the pathogenesis of DISH [27]. A review suggested that biallelic pathogenic variants of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), dentin matrix protein 1 (DMP1), and hemizygous or heterozygous phosphate regulating endopeptidase homolog, X-linked (PHEX) mutations are genetic factors that place patients at risk for DISH and OPLL [28]. As ENPP1, DMP1, and PHEX all induce fibroblast growth factor 23 (FGF23)-related hypophosphatemia, it can be hypothesized that common pathophysiological mechanisms may favor spinal ligament ossifications.

Over the last two decades, DISH has been strictly associated with DM and the metabolic syndrome (MS), which lead to several metabolic abnormalities. However, their direct or causal relationships have not been defined yet [29]. Nowadays, the only recognized comorbidity is the association between DISH and a higher body mass index (BMI) [30].

The frequency of obesity, DM and MS—an acknowledged risk factor for coronary artery disease, also associated with increased mortality and morbidity [31]—has significantly increased in the western world. Not unexpectedly, two studies have shown that DISH patients have a higher incidence of risk factors for stroke and future coronary events [31, 32]. If the presumed association between DISH, an aging population, and the increasing incidence of MS is confirmed, the prevalence of DISH can be expected to rise proportionally, thus making it endemic in elderly people.

To describe the clinical complexity of DISH, this review has been focused on its extraspinal features.

Conditions associated with DISH:

(1). Non-insulin-dependent DM.

(2). Obesity.

(3). High waist circumference (WC) ratio.

(4). Dyslipidemia.

(5). Hypertension (HTS).

(6). Hyperuricemia.

(7). Hyperinsulinemia.

(8). Elevated insulin-like growth factor-1 (IGF-1).

(9). Lung disease.

(10). Dysphagia.

MS and cardiovascular risk

The MS, characterized by impaired glucose/insulin regulation, obesity/abnormal abdominal fat distribution, dyslipidemia, and HTS [33], represents a crucial risk factor for the development of type II DM, and cardiovascular disease (CVD) [34, 35].

In 1996, Vezyroglou et al. [36] compared patients with DISH to patients without DISH, matched on age, sex, and BMI. This study showed that the rate of metabolic diseases including DM, dyslipidemia, and hyperuricemia was higher in patients with DISH than in those without DISH. Moreover, a significantly higher prevalence of obesity and first-degree relatives with DM or HTS was found in patients in the early phase of DISH (younger than 50 years of age) compared to patients of similar age with OA [29]. These patients were also more likely to develop DM during follow-up [29]. Serum IGF-1, insulin, and growth hormone (GH) levels are significantly higher in patients with DISH than in normal controls [37, 38]. Notably, basal serum insulin levels were significantly elevated in DISH patients with a BMI > 28 kg/m^2, with a strong positive correlation between BMI values and serum insulin concentrations but not with basal serum GH or IGF-1 levels [39]. Corticosteroids and/or non-steroidal anti-inflammatory drug-related improvement of DISH symptoms (reduction in muscle pain and joint stiffness, increase in spinal range of motion) resulted in lower serum GH levels, but IGF-1 levels were unchanged, suggesting that elevated GH, and not IGF-1, contributed to the progression of clinical symptoms in DISH [37].

In support of the role of endocrine-metabolic abnormalities in DISH, a retrospective study of whole spine computed tomography (CT) scans from 1,815 polytrauma patients recently confirmed that DISH is associated with obesity, DM, HTS, and aortic calcification [40].

In line with these results, a vast body of studies supported the finding that patients with DISH, compared with non-DISH patients, express higher BMI and/or WC [41, 42].

Increased body fat, mainly visceral adipose tissue (VAT) surrounding the intra-abdominal organs, has been associated with impaired glucose/insulin regulation and dyslipidemia [43, 44] and represents a major predictor for cardiovascular events [45].

CT examination of abdominal fat surface area, a known marker for MS, revealed that they are significantly larger in DISH subjects than in controls [46].

VAT may be a possible contributor to the pathogenesis of the spinal calcifications characteristic of DISH through the expression of inflammatory mediators. Studies consistently demonstrated that VAT produces bioactive polypeptides, collectively named "adipokines", such as leptin and adiponectin (ADP), and inflammatory molecules, including tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [47]. It has been hypothesized that adipokines could play a role in the pathogenesis of DISH, as animal studies demonstrate that leptin promotes osteoblast numbers and activity in mice [48]. Moreover, hereditary obese rats showed an altered leptin receptor gene associated with the ossification of spinal ligaments (OSL), a condition similar to DISH [49]. More recently, two studies evaluated the adipokine levels in patients with DISH [50, 51]. Tenti et al. [50] detected significantly higher serum leptin levels in DISH patients (with or without diabetes) compared with patients affected by lumbar OA ($P < 0.0001$ and $P < 0.005$, respectively). Furthermore, a significant decrease in ADP was observed in patients with DISH associated with diabetes *vs.* OA patients ($P < 0.05$). Mader et al. [51] found that serum ADP values negatively correlated with serum insulin and insulin resistance levels. In addition, in the same group of DISH patients, higher ADP values positively associated with serum cholesterol and low-density lipoprotein (LDL) levels and with the extent of bony bridges ($r = 0.245$, $P = 0.02$).

The first study designed to assess the risk of MS in patients with DISH diagnosed by using accepted criteria (Resnick and Niwayama's [13] classification), was published by Mader et al. [30] in 2009. MS was significantly more prevalent in DISH patients than in the control group (age and sex-matched; $P = 0.001$ and $P = 0.007$, respectively). The odds ratio (OR) for patients with DISH diagnosed according to the World Health Organization (WHO)-MS [52] was 3.61, and for DISH diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP)-MS criteria [53] was 3.88. DISH patients showed a higher risk to develop coronary heart disease (CHD; as per Framingham risk scoring system; $P = 0.004$), conferring a higher 10-year CHD risk relative to patients without DISH ($P = 0.007$) [30].

A 10-year follow-up evaluation of participants without known CVD disease enrolled in the previous study cohort showed that the incidence of myocardial infarction (MI) was significantly higher in the DISH group ($P = 0.005$) than in the control non-DISH group [54]. It should be noted that CVD incidence was higher than expected. Specifically, using the Framingham score, 28.6% of the DISH patients were expected to develop CVD after ten years, while the study demonstrated that nearly 39% of them really developed CVD at the end of a 10-year follow-up period. The finding of a higher-than-expected actual MI incidence suggests that DISH may be an independent CVD risk factor. Further support to this hypothesis came from the study of Oudkerk et al. [55], who demonstrated that subjects with DISH had a significantly higher risk of having coronary artery calcifications compared to subjects without DISH [OR 1.37, 95% confidence interval (CI) = 1.05–1.78, $P = 0.019$; OR 1.27, CI = 1.05–1.78, $P = 0.019$] after correction for age, gender, race, chronic obstructive pulmonary disease (COPD) and atherosclerotic risk factors.

A large retrospective cohort study in Taiwan found significantly higher prevalence rates of stroke, HTS, diabetes, and hyperlipidemia in patients with DISH compared with age- and sex-matched controls. In particular, DISH conferred a 1.68 times higher risk of developing stroke independently of the presence of HTS [56].

In line with this result, a prospective cohort study including 4,624 individuals demonstrated that DISH was associated with a 55% increase in ischaemic stroke after correction for age, sex, and cardiovascular risk factors. No other independent relationships were found between DISH and MI, vascular death, or all-cause mortality [57]. In the same cohort, individuals with DISH have more thoracic aortic calcification (TAC), which may help to explain how DISH relates to ischaemic stroke [58]. It was hypothesized that TAC can influence arterial stiffness and hence the normal compressive (Windkessel) function of the aorta that

converts the phasic systolic inflow produced by ventricular ejection into a more continuous outflow to peripheral vessels.

The association between MS and DISH has been recently confirmed by a retrospective analysis of clinical data from 327 consecutive subjects undergoing health medical checkup examinations [59]. This study demonstrated that MS was more frequently detected in the DISH group (28.9%) than in the non-DISH group (16.0%; $P = 0.045$) with an OR of 2.0 (95% CI = 1.0–3.7; $P = 0.004$).

Accordingly, the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik Study) [60] —a large population-based cohort study of older Icelanders comprising 5,321 participants aged 68–96—highlights the association between DISH and MS [OR 2.12; 95% CI = 1.69–2.64; $P = 3.9 \times 10^{-11}$] also in elderly individuals.

Dysphagia

The pathological new bone formation, mainly involving the anterior longitudinal ligament of the spine, may cause dysphagia, perceived as difficulty swallowing, sometimes associated with foreign body sensation, odynophagia, salivary stasis, and dysphonia [61]. The most common level of spine involvement in producing dysphagia is C5–C6, with C2–C3 less commonly affected [62].

The estimated incidence of cervical dysphagia due to DISH is around 7:100,000 inhabitants per year [63]. A recently updated systematic review of 138 articles (112 case reports and 26 case series) described 419 patients with dysphagia and/or airway obstruction caused by cervical DISH. Patients mainly were males, 85.4% and had a mean age of 67.3 years [64].

In addition to the direct mechanical obstruction due to the bone proliferation in the anterior part of the cervical spine, the inflammation of the soft tissue adjacent to the esophagus, together with esophageal and pharyngeal muscle spasm [65], and recurrent nerve palsies elicited by the hyperostosis, may also contribute to the development of dysphagia [66].

Plain radiographs are usually sufficient to make a DISH diagnosis. Still, in DISH-related dysphagia, CT and magnetic resonance imaging (MRI) help to evaluate the extent of the hyperostosis, its location relative to the esophagus, and the presence of spinal stenosis with compression and myelomalacia [66].

Treatment for DISH is based on symptomatic relief of symptoms, while anterior cervical resection of osteophyte may be considered in patients with airway obstruction and/or dysphagia, in whom a conservative approach was ineffective [67].

The complication rate after surgery was 22.1%, and 12.7% occurred within 1 month after intervention [64]. Esophageal injury due to large osteophytes and esophagus adhesion to other cervical fascia produced by the local inflammation may be a surgery complication. The dysphagia improved in 95.5% of surgically treated patients but recurred in 4% of them after a mean follow-up of 3.7 years [64].

Respiratory disturbances

The bony bridges between vertebral bodies and the involvement of the sternocostal and costochondral junctions can lead to a limited expansion of the thoracic cage that may affect ventilation.

In support of this hypothesis, a study recruiting a cohort of lung cancer screening participants demonstrated that individuals with DISH diagnosed on CT scans presented lower CT-measured lung volumes [68].

The same authors studied 1,784 former and current smokers who, after a complete post-bronchodilator spirometry, did not meet the spirometric criteria for the diagnosis of COPD [69]. A restrictive spirometric pattern (RSP) was described if patients had a forced expiratory volume in 1s (FEV1) to forced vital capacity (FVC) ratio > 0.7 with an FVC < 80%. The results showed that DISH was significantly associated with RSP (OR 1.78; 95% CI = 1.22–2.60; $P = 0.003$) after adjusting for potential intrinsic and extrinsic causes of restrictive lung function [69].

Dyspnea is associated with dysphagia in 14% patients with anterior cervical osteophytosis [70], while the literature reports only a few cases of patients with dyspnea without associated dysphagia [71].

Aspiration pneumonia, usually associated with dysphagia, is rare but can be life-threatening. Of five patients with dysphagia caused by DISH, three showed bolus aspiration into the airways, mainly in the post-swallowing phase. The pathogenetic alterations affecting swallowing mechanisms were compression of the pharyngeal lumen with abnormal epiglottic tilt, incomplete openings of the upper esophageal sphincter, and epiglottic/vallecula stasis [72].

Neurological symptoms

DISH neurological complications are uncommon, being seen in around 0.4% of the patients [73]. A retrospective analysis of 74 cases of DISH [74] revealed that 11 patients had presented with progressive spinal cord or cauda equina compression. The neurological complication occurred in nine cases due to the OPLL and in two cases due to the ossification of the ligamentum flavum (OLF). The thoracic spinal cord and nerve root compression may lead to numbness, extreme weakness, and even paralysis in the lower extremities. Of note, the association of bladder and/or bowel loss of control requires immediate therapeutic interventions. The thoracic spinal stenosis slowly progresses, mainly driven by the stimulation of mechanical stress [75]. Unlike other types of spinal conditions, thoracic spinal stenosis often does not respond well to non-surgical treatment, while decompressing surgery is an effective treatment approach. The recent study of Dong et al. [76] suggested that posterior decompression and fusion surgery could achieve satisfactory clinical outcomes, which were comparable between DISH and non-DISH patients. Although ossification in DISH occurs primarily in the anterior longitudinal ligament, the involvement of the posterior longitudinal ligament in the cervicothoracic spine can result in ankylosis, which definitely changes the biomechanics of the spine. This spinal imbalance increases susceptibility to injury, even low-energy trauma, leading to fractures with an increased risk of neurological sequelae and difficulty with tracheal intubation if required.

Cervical myelopathy can occur due to spinal canal narrowing caused by OPLL or OLF compression and manifests with difficulty in walking and weakness in all four limbs [77]. Early surgical intervention helps to achieve a better outcome in patients with neurodeficiency and prevents further complications.

Finally, a cross-sectional study identified an association between DISH and lumbar spinal stenosis requiring surgery, a condition characterized by neurological deficits in the lower extremities, intolerable leg pain, and bladder or bowel dysfunction [78].

Conclusions

DISH is a systemic disease characterized by progressive calcification and ossification of ligaments and entheses along the spine and with extra-spinal involvement. This disease often goes unnoticed among the affected individuals, and for this reason it has not yet been studied so in depth. DISH may suggest the presence of underlying metabolic imbalances and associated CVD. The prevalence of DISH in Western countries is set to increase due to the widespread presence of its risk factors: increased life expectancy, obesity, DM, and HTS. DISH involves the spine, peripheral joints and entheses, causing entheseal ossification and/or calcification around peripheral joints, in particular of tendons, ligaments, and joint capsules. Several complications of the disease such as higher cardiovascular risk, complex spinal fractures, post-surgical heterotopic ossifications, difficult intubation, aspiration pneumonia, and dysphagia have been described. Unfortunately, the current DISH classification criteria allow identifying the diagnostic feature late in the illness course. Research and clinical advantage may derive from identifying initial disease phases by detecting the early inflammatory changes around and within the axial and peripheral skeleton with MRI. Focusing on individuals with MS or increased VAT as at-risk populations may help clarify possible causal relationships and early pathogenetic mechanisms to implement targeted therapies.

Abbreviations

ADP: adiponectin

BMI: body mass index

CT: computed tomography

CVD: cardiovascular disease

DISH: diffuse idiopathic skeletal hyperostosis

DM: diabetes mellitus

GH: growth hormone

HTS: hypertension

IGF-1: insulin-like growth factor-1

MI: myocardial infarction

MS: metabolic syndrome

OA: osteoarthritis

OPLL: ossification of the posterior longitudinal ligament

OR: odds ratio

VAT: visceral adipose tissue

Declarations

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Author contributions

FA and RM: Conceptualization, Writing—original draft, Writing—review & editing, Supervision. AA: Writing—original draft, Writing—review & editing. SB: Writing—review & editing, Supervision. All authors, except Professor Mader read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Consent to participate

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