

## Extraskelletal symptoms and comorbidities of diffuse idiopathic skeletal hyperostosis

Rabia Terzi

Rabia Terzi, Derince Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Kocaeli 41 300, Turkey

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Correspondence to: Rabia Terzi, MD, Derince Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Orhan Mh. Devran Caddesi. Bağkule Evleri B2 blok İzmit, Kocaeli 41 300, Turkey. [drrabia1@yahoo.com](mailto:drrabia1@yahoo.com)

Telephone: +90-505-3515572

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established, limited data on extraskelletal signs and comorbidities are available. In this article, we review extraskelletal symptoms and associated comorbidities in patients with DISH in the light of the literature.

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### Abstract

Diffuse idiopathic skeletal hyperostosis (DISH) is a non-inflammatory disease characterized by calcification and ossification of soft tissues, mainly entheses and spinal ligaments. The clinical presentation primarily includes spinal involvement-induced pain and range of motion. Although rare, life-threatening gastrointestinal, respiratory or neurological events or severe morbidity due to bone compression on the adjacent structures may develop. There is a limited amount of data on DISH-related events in the literature. In recent years, comorbid metabolic disorders are of great interest in patients with DISH. The early diagnosis of these conditions as well as rare entities allows an effective multidisciplinary approach for the treatment of DISH. In this article, we review extraskelletal symptoms and associated comorbidities in patients with DISH.

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**Key words:** Diffuse idiopathic skeletal hyperostosis; Swallowing; Respiratory symptoms; Neurological symptoms; Comorbidities

**Core tip:** Although diffuse idiopathic skeletal hyperostosis (DISH)-related skeletal symptoms are well-

### INTRODUCTION

Diffuse idiopathic skeletal hyperostosis (DISH) is a non-inflammatory disease characterized by calcification and ossification of soft tissues such as ligaments, tendons and fasciae with an unknown etiology<sup>[1]</sup>. The prevalence which increases with age<sup>[1]</sup> has been reported to be 2.8% and 2.6% in men and women aged  $\geq 40$  years, respectively<sup>[2]</sup>. The diagnosis is based on the presence of involvement of at least four contiguous thoracic vertebral segments, preservation of intervertebral disc spaces, and the absence of apophyseal joint degeneration or sacroiliac inflammatory changes<sup>[3]</sup>.

Clinical manifestations of the disease vary depending on the involvement site. It may also present asymptotically. The axial skeleton is the most commonly affected site at 70%. Thoracic involvement is the most common manifestation of DISH, while the cervical spine is minimally involved<sup>[4,5]</sup>. In addition, DISH is not limited to axial skeleton involvement. Other anatomical structures affected by the disease include the pelvis, patella, calcaneus bone or olecranon<sup>[5]</sup>. The majority of symptoms occurs due to altered biomechanics of the skeleton, leading to pain, stiffness and restricted range of motion (ROM) of the axial or peripheral joints. Moreover, respiratory, gastrointestinal and neurological symptoms may develop

due to bone compression of the adjacent structures<sup>[6,7]</sup>. The incidence of metabolic disorders, such as metabolic syndrome, diabetes and obesity, has been reported to be increased in patients with DISH<sup>[8]</sup>. Therefore, it is of the utmost importance that symptoms other than pain and limited ROM and comorbidities should be identified and a multisystemic therapy should be tailored for each patient. In this article, we review extraskelatal symptoms and associated comorbidities in patients with DISH.

## SWALLOWING AND RESPIRATORY SYMPTOMS

Cervical involvement has been reported to be 75% in patients with DISH<sup>[9]</sup>. Cervical osteophytes are usually asymptomatic<sup>[10]</sup>. The swallowing function is primarily affected in cases of symptomatic manifestations. The size and location of the bone spurs may vary. In the presence of upper cervical spine involvement (C3-4), laryngeal functions are mostly affected<sup>[11]</sup>. However, spasm or obstruction of the esophageal sphincter may occur in the presence of distal involvement<sup>[12]</sup>. McCaffrey showed that there was no relationship between the size of the bone spurs and severity of the symptoms<sup>[13]</sup>. Dysphagia is the most common complaint in these patients. Dysphagia typically results from esophageal compression by the osteophytes exerting a mass effect<sup>[14]</sup>, recurrent laryngeal nerve injury-related neuropathy<sup>[15]</sup>, and esophageal fibrosis and inflammation secondary to osteophyte irritation<sup>[16]</sup>. As the incidence of DISH increases with age, dysphagia should be considered particularly in the elderly<sup>[17]</sup>.

Furthermore, tracheal compression of the giant osteophytes may lead to acute or progressive airway obstruction. Caminos *et al*<sup>[18]</sup> reported a case admitted with acute onset respiratory failure and diagnosed with DISH. The patient suffered from shortness of breath in the supine position. Cervical lateral X-ray revealed a large osteophyte which compressed the trachea. The authors concluded that DISH should be kept in mind particularly in elderly patients with unexplained respiratory distress<sup>[18]</sup>. In another study, Nelson *et al*<sup>[19]</sup> reported three cases requiring tracheotomy due to acute airway obstruction. Gokce *et al*<sup>[20]</sup> also described a case of DISH with postoperative stridor and respiratory distress due to cricoarytenoid joint fixation and right vocal cord paresis following total knee arthroplasty. Respiratory distress was reported to be induced by venous compression, nerve compression, cricoarytenoid joint fixation, post-cricoid ulceration and edema<sup>[21]</sup>.

In a study including 204 patients with DISH between 1980 and 2009, Verlaan *et al*<sup>[8]</sup> reported dysphagia and airway obstruction in the study population. However, the authors found no relationship between age and the degree of dysphagia or airway obstruction. One or more of the imaging studies including cervical X-ray, barium swallow, computed tomography (CT), laryngoscopy and magnetic resonance imaging (MRI) were performed.

As DISH is mostly seen in the elderly, endoscopic in-

spection of the upper gastrointestinal system is critical in the differential diagnosis of malignancies. However, caution should be exercised during endoscopy with a gentle pressure. Otherwise, iatrogenic pharyngoesophageal perforation may occur<sup>[22]</sup>. Non-surgical treatments include dietary modification (fluid and soft food intake), anti-reflux medications, gastroprotectants and percutaneous endoscopic gastrostomy tube placement<sup>[8]</sup>. On the other hand, surgical treatment options are anterolateral, lateral or transpharyngeal resection of the ossification. Also, spinal decompression, discectomy and spinal fusion are additional surgical procedures. There are no statistically significant differences in the sex, duration of symptoms, and the number of affected vertebrae between surgically and non-surgically treated patients<sup>[8]</sup>. However, a higher number of younger patients with severe symptoms were primarily operated on. Respiratory and swallowing functions were improved in most patients following surgery<sup>[8]</sup>.

## NEUROLOGICAL SYMPTOMS

Neurological symptoms which are rarely seen include decreased flexibility of the spine and narrowed spinal canal-related myelopathy due to anterior and posterior longitudinal ligament calcification<sup>[23]</sup>. Myelopathy is often associated with narrowing of the lower cervical vertebral canal<sup>[23]</sup>. Lumbar spinal canal stenosis was also reported in the literature<sup>[24]</sup>. The craniocervical junction is rarely involved. It is mainly caused by atlantoaxial dislocation or pseudoarthrosis between the spinal process of the axis and the posterior tubercle of the atlas<sup>[25]</sup>. In addition, there is a case of DISH with retro-odontoid pseudotumor-induced progressive myelopathy in the literature<sup>[26]</sup>. Retro-odontoid pseudotumors can be defined as lesions caused by inflammatory granulation or reactive soft tissue hypertrophy from chronic atlantoaxial subluxation. These patients may present with post-traumatic neurological symptoms<sup>[26]</sup>. Eser *et al*<sup>[27]</sup> described a surgically-treated case of central cord syndrome after a minor trauma. The patient had no cervical dislocation or fracture. However, MRI demonstrated spinal cord edema and myelomalacic segments. Koizumi *et al*<sup>[28]</sup> reported another case of myelopathy due to multilevel cervical canal stenosis. Such patients may suffer from spinal fractures and neurological deficit after a minor trauma. These fractures can be easily overlooked since they progress to a neurological deficit over time with a limited initial clinical presentation. This can be attributed to the fact that the mortality rate of DISH patients with spinal fractures has been reported to be nearly 20%<sup>[29]</sup>. Vengust *et al*<sup>[30]</sup> reported a case of DISH in whom post-trauma fracture dislocation developed at the third and fourth cervical vertebrae. Respiratory failure was triggered by vocal cord paralysis due to laryngeal nerve entrapment at six months<sup>[30]</sup>.

In addition to neurological complications, the incidence of stroke was reported to be increased in patients with DISH<sup>[31]</sup>. In a study including a total of 90 patients, 45 with DISH and 45 with cervical spondylosis, MRI

revealed a higher incidence of infarction in patients with DISH. Magnetic resonance angiography also showed a higher incidence of major cerebral artery stenosis and occlusion in these patients. Based on these data, the authors concluded that patients with DISH had an increased risk for stroke as well<sup>[31]</sup>. In another report, a 53-year-old case with DISH was admitted with motor and sensory polyneuropathy<sup>[32]</sup>. It was associated with the metabolic disturbance in this patient population. Moreover, another case with DISH presenting with thoracic outlet syndrome-associated findings is available in the literature<sup>[33]</sup>.

### MISCELLANEOUS SYMPTOMS

Other symptoms of DISH include dysphonia, weight loss, odynophagia, reflux disease, snoring, aphonia, choking, pharyngeal perforation, difficult intubation and aspiration pneumonia<sup>[8]</sup>.

### DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS-ASSOCIATED METABOLIC COMORBIDITIES

The relationship between DISH and metabolic status has been shown. The incidence of DISH is higher in patients with diabetes, hypertension, hyperlipidemia, hyperinsulinemia, metabolic syndrome or obesity<sup>[34]</sup>. Vezyroglo *et al*<sup>[35]</sup> determined that metabolic abnormalities occurred in 70% of patients diagnosed with DISH and 45% in the control group. Hyperlipidemia and hyperuricemia associated with diabetes have been found frequently in patients diagnosed with DISH. Combined metabolic features of diabetes mellitus and dyslipidemia, diabetes mellitus and hyperuricemia, or diabetes mellitus and dyslipidemia and hyperuricemia were shown to be the main risk factor for DISH<sup>[35]</sup>. Mader<sup>[35]</sup> reported that patients diagnosed with DISH have a higher metabolic syndrome rate than the control group. Eckertova *et al*<sup>[36]</sup> reported that non-esterified fatty acids, insulinogenic index and insulin/C-peptide ratio decrease in patients diagnosed with nondiabetic DISH. These patients have identified impaired pancreatic beta-cell stimulation and increased hepatic insulin extraction. Eckertova *et al*<sup>[36]</sup> suggested that if these conditions persist for a long time, it might lead to a decreased ability of insulin to maintain a normal serum glucose level and consequently to insulin resistance which is highly prevalent in symptomatic DISH patients.

### DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS-ASSOCIATED CARDIOVASCULAR COMORBIDITIES

It has been reported that hypertension, atrial fibrillation, left ventricular hypertrophy and peripheral arterial disease increased<sup>[10,37,38]</sup> in patients diagnosed with DISH. Mader *et al*<sup>[16]</sup> reported that the 10 year coronary heart

disease risk of patients with DISH is significantly higher than the control group. Zincarell *et al*<sup>[39]</sup> suggest that DISH prevalence was found to be 30.3% in patients with severe cardiovascular disease. A lot of studies reported that DISH carries a risk for stroke and cerebrovascular diseases.

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