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Diffuse idiopathic skeletal hyperostosis: Etiology and clinical relevance

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A B S T R A C T

Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic bone-forming condition characterized by the presence of at least three bony bridges at the anterolateral spine. The aim of this review was to address the present state of pathophysiological knowledge, the clinical relevance, and diagnosis of DISH. The pathogenesis of DISH is currently unknown. The presence of DISH has been associated with older age, male sex, obesity, hypertension, atherosclerosis, and diabetes mellitus. Because the new bone forms mainly at entheseal sites, local fibroblasts, chondrocytes, collagen fibers, and calcified matrix are probably influenced by genetic, vascular, metabolic, and mechanical factors. Diagnosing the presence of DISH is of clinical importance, because the risk of a spinal fracture increases and associations with the metabolic syndrome, coronary and aortic disease, and respiratory effects are strong. Unravelling the pathogenesis of DISH can impact the field of regenerative medicine and bone tissue regeneration.

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Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic condition characterized by the presence of at least three bony bridges at the anterolateral spine opposite to the aorta (Fig. 1) [1,2]. Ossification at the location of entheses in the peripheral skeleton may also be present, for example at the shoulders, elbows, wrists, pelvis, hips, knees, and ankles [3]. The prevalence of DISH is reported between 2.9% and 42.0% depending on the classification criteria used, and the presence of risk factors in the studied population [4–6]. By the beginning of the 20th century, multiple authors have described the phenomenon of "hyperostosis in the spinal column," which later became known as Forestier's disease, as a result of the landmark paper by Forestier and Rotes-Querol in 1950 [7–9]. The term – diffuse idiopathic skeletal hyperostosis – which is widely used now, was introduced in the mid-70s of the last century by Resnick et al. to summarize their radiological findings in 21 cases [10]. Their study subjects did not only have typical spinal hyperostosis, but also showed manifestations in the peripheral skeleton at the knees, heels, and pelvis [10]. Resnick and coworkers decided to further investigate the spinal and extraspinal manifestations, and they formulated a name for the condition by describing what they observed. DISH is located diffusely throughout the body, the pathogenesis is not yet understood (idiopathic), the skeleton is affected, and abundant bone growth is present (hyperostosis). This descriptive name will likely not be replaced until more is known about the pathogenesis of DISH. The aim of this review is to address the current state of pathophysiological knowledge with some future research directions and to appraise the clinical relevance of DISH.

How to diagnose DISH

The first report in literature regarding hyperostosis of the spine dates back to the end of the nineteenth century and many descriptions of the condition followed [7,8,11,12]. In 1976, Resnick and

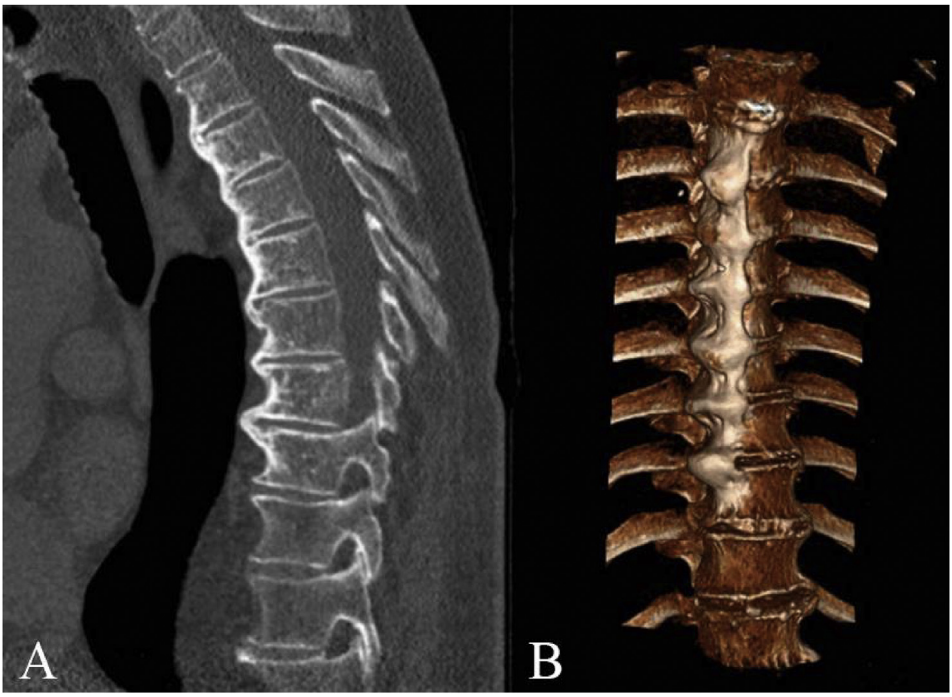

Fig. 1. Computed tomography scan of a 70-year-old male patient. In A, the sagittal reconstruction is shown, clearly demonstrating bridges of bone over more than four vertebral bodies. In B, the three-dimensional reconstruction demonstrates the flowing cortical new bone.

Niwayama published their strict radiographic criteria to diagnose DISH: "(a) The presence of 'flowing' calcification and ossification along the anterolateral aspects of at least four contiguous vertebral bodies with or without associated localized pointed excrescences at the intervening vertebral body-disc junctions. (b) A relative preservation of disc height in the involved areas and the absence of extensive radiographic changes of 'degenerative' disc disease, including vacuum phenomena and vertebral body marginal sclerosis. (c) Absence of apophyseal joint bony ankylosis and sacroiliac joint erosion, sclerosis or bony fusion." [1] These criteria were chosen by authors to ensure that subjects included in their study were definite cases of DISH and that subjects with other spinal ankylosing diseases (*i.e.,* ankylosing spondylitis) were excluded. Although Resnick had stated in his previous work in 1975 that DISH is a condition not only of the spine, authors specifically investigated patients with spinal manifestations of DISH; hence, the criteria were only defined for spinal manifestations of DISH [1,10]. Currently, these criteria by Resnick and Niwayama are the most frequently used criteria in literature, even though they describe an advanced stage of DISH and exclude peripheral manifestations. A literature review on the criteria available for DISH revealed 24 articles describing different sets of criteria to diagnose DISH [13]. The most essential component to diagnose DISH was the presence of new bone, bridging at the anterior part of multiple vertebrae, as all authors included this phenomenon in their criteria. This finding was supported by a Delphi exercise in 2013, in which seven specialists with an interest in DISH developed a list of potential criteria parameters for DISH [14]. This list was subsequently presented to 39 rheumatologists and orthopedic surgeons worldwide for their support, if the item should be a criterion for DISH. Also in this study, consensus was only reached for the presence of enlarged bony bridges in the spine.

When comparing available DISH criteria in the literature, differences between authors included how many vertebral levels had to be involved, completeness of a bone bridge, relative preservation of the intervertebral disc/apophyseal joints/sacroiliac joints, presence of peripheral manifestations, and the diagnostic method used, with recently more interest in CT [13,15]. The progressive nature of DISH was only incorporated in the criteria of 11 studies. Unfortunately, these criteria – which more accurately reflect the progressive nature of DISH – are not frequently used in DISH research, while the more limited Resnick criteria are used. All 24 sets of new criteria for DISH were not originally designed to develop new standardized criteria, but were merely used as an outcome measure in research, such as association research [13].

Recently, a study was designed just to develop and validate new criteria for the early phase of DISH [16]. As the Resnick criteria are the most commonly used criteria to diagnose DISH, the pre-DISH criteria from this latest article can be added to the Resnick criteria to investigate DISH as a progressive condition.

The exclusion criteria regarding the quality of the intervertebral disc, apophyseal joints, and sacroiliac joints were described by Resnick and Niwayama to ensure that they had selected a study group without confounding other diseases [1]. However, in a clinical setting DISH and other spinal conditions such as ankylosing spondylitis (AS) can co-occur [17]. If comorbidities are regarded as a reason to reject the diagnosis, this will lead to a higher specificity (higher true negative rate) of a condition in a population. In rheumatological research, a clear distinction is made between criteria used in the research setting, referred to as "classification criteria" and criteria for the clinical setting, referred to as "diagnostic criteria." [18] According to the American College of Rheumatology, classification criteria need to define a homogeneous group, and thus require very high specificity with an accepted loss in sensitivity to avoid confounding [18]. Diagnostic criteria are broad with a high sensitivity and medium-to-high specificity. At the moment, no distinction is made between establishing DISH in the clinical or research setting and as a result, 39 cases are described in literature demonstrating the potential co-occurrence of DISH and AS in the clinical setting [17]. For this reason, the exclusion criteria by Resnick and Niwayama may not be ideal in the clinical setting, but are of value in the research setting. In a research setting, it is advised that cases with signs of DISH and comorbidities as described in the exclusion criteria by Resnick and Niwayama should be excluded from the research population completely, to avoid confounding in the control group.

Etiology

The pathogenesis of DISH is currently unknown. The formation of new bone is the most important characteristic of DISH, and thus researchers have developed several hypotheses about how and why this new bone is formed [19]. On a microscopic level, the new bone forms a bone bridge from one vertebral body to the adjacent vertebral body [20]. The new bone is in continuum with the upper and lower vertebral body and contains mostly cortical and some cancellous bone. Woven bone is present, suggesting an ongoing remodeling in the new bone formation. Because the new bone forms mainly at entheseal sites, local fibroblasts, chondrocytes, collagen fibers, and calcified matrix are probably influenced by genetic, vascular, metabolic, and mechanical factors [19,21]. Unravelling the pathogenesis of DISH can impact the field of regenerative medicine and bone tissue regeneration.

Epidemiological associations

The presence of DISH has been associated with older age, male sex, obesity, hypertension, atherosclerosis, and diabetes mellitus (Fig. 2) [4,5,22].

The correlation between increasing age and the presence of DISH has been described in numerous studies describing the prevalence and associations with DISH (Fig. 3) [4–6,23–39]. Multiple authors have compared the mean age of a group with DISH to the mean age of a group without DISH and 12 of the 13 studies statistically analyzing age-described significant differences ($p < 0.006$) [4,5,25,27–29,32,33,35–37,39]. In addition, the prevalence of DISH reported per decade of age also showed a strong increase in prevalence [4–6,23,24,26–28,30,34,37,38]

The male sex is significantly associated with increased prevalence of DISH in numerous articles [5,6,26,28,29,33,37,40]. A male-female ratio of up to 7 - 1 has been reported; however, study groups were small and correction for confounding factors was not always performed. With older age, the difference in prevalence of DISH between male and female subjects also appears to increase, which is also demonstrated by diverging lines in Fig. 3. Four other studies lacked significant results comparing DISH in male and female subjects, most likely due to selection (younger study subjects, only small study groups or selection of cases for a case-control study) [24,31,39,41].

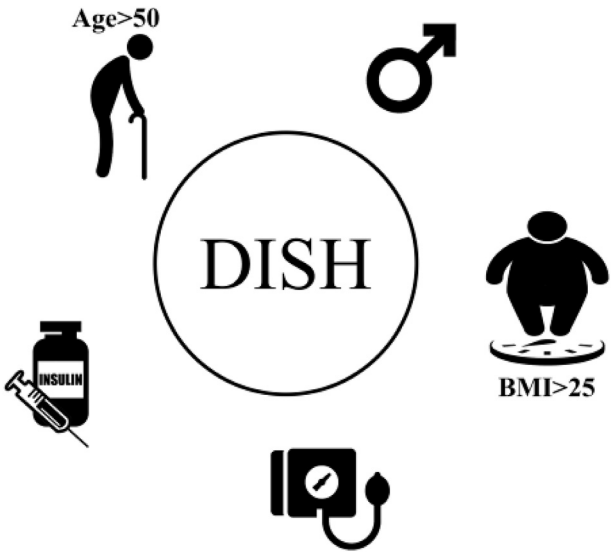

Fig. 2. DISH is associated with older age, male sex, obesity, hypertension, and diabetes mellitus.

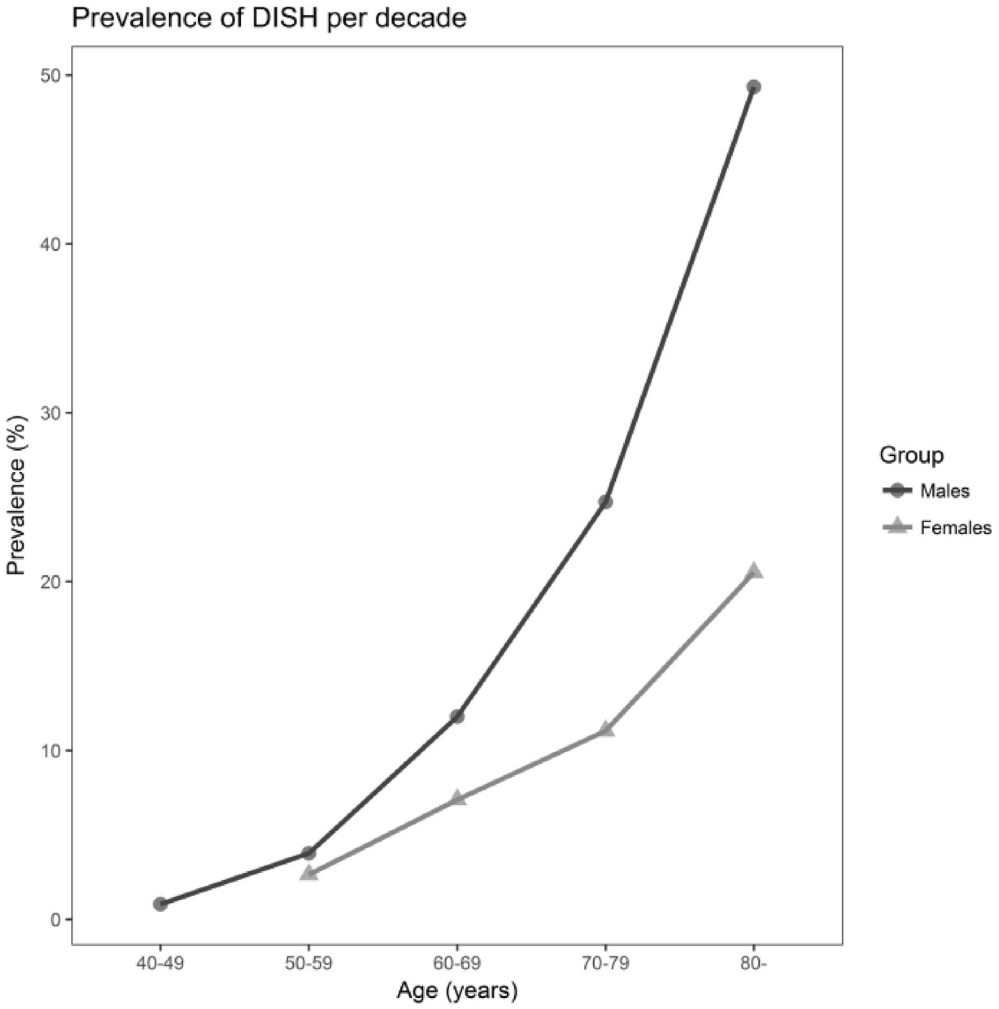

Fig. 3. Prevalence of DISH based on the data of studies describing the prevalence of DISH. The prevalence was calculated using data from seven different studies. Five studies presented their findings separate for men and women and two studies described only one sex (Julkunen 1971, Bloom 1984, Cassim 1990, Kiss 2002, Pappone 2005, Holton 2011, and Hirasawa 2016). Most authors used Resnick criteria to diagnose DISH on conventional imaging and studies were performed in Finland, Israel, South Africa, Hungary, Italy, USA, and Japan.

Obesity is another important risk factor for DISH. In all 11 studies investigating the relation between DISH and an increased body mass index (BMI), an elevated BMI was found in patients with DISH [4,25,27–29,31,32,35,37,39,42]. After correcting for confounders in a regression model, the significant correlation between the presence of DISH and an increased BMI remained [28,35,42].

Hypertension is reported to be more frequently present in subjects with DISH compared to subjects without DISH, but statistical significance has only been reached in two out of five studies [4,31,35,39,42]. Systolic blood pressure was significantly higher in the DISH population (144–151 mmHg) compared to the non-DISH population (139–145 mmHg) in two studies [4,35].

Diabetes mellitus is significantly more common in patients with DISH when compared with patients without DISH according to seven studies [24,25,27,29,42–44]. Furthermore, six other studies described an increase of diabetes mellitus in DISH, but could not support results with significant statistical testing [4,35–37,39,45].

The metabolic syndrome is also strongly correlated with the presence of DISH [31,35]. The metabolic syndrome is diagnosed based on waist circumference, triglyceride level, high-density lipoprotein level, blood pressure (or the use of medication to regulate blood pressure), and fasting glucose [31]. Hypertriglyceridemia (>150 mg/dl or >2.2 mmol/l) is more common in patients with DISH, but was not statistically significant in six studies [31,35,39,42,43,45]. The prevalence of hypercholesterolemia is comparable between patients with and without DISH [39,42]. When comparing blood levels of cholesterol, high-density lipoprotein, and low-density lipoprotein, no significant differences were found between patients with DISH and patients without DISH in four studies [31,35,43,45]. Further research should investigate if waist circumference, blood pressure, and fasting glucose are the three most important parameters that lead to a strong association between metabolic syndrome and DISH. These biomarkers could potentially be used to diagnose or predict the development of DISH.

Cardiovascular diseases (mainly ischemic heart disease and stroke) were reported equally in patients with and without DISH [29,35,37,42]. In contrast, aortic sclerosis was significantly more often present in the DISH group as compared to a control group (55.4% vs 21.7%) even after correction for age and sex [33]. Aortic calcifications were more frequently observed in DISH subjects after correction for age and BMI [35]. Coronary artery calcifications were also associated with the presence of DISH, even after correction for age, gender, and race [46].

An association has been found between DISH and lower lung volumes [47]. Authors hypothesized that spinal ankylosis also extends toward articulations with ribs, resulting in a stiff thoracic cage. This theory is further supported by the association that was found between the presence of DISH and a restrictive spirometric pattern [48]. Clinicians should be aware that DISH could be the cause of reduction in pulmonary function, potentially also contributing to an increased risk for pneumonia in the elderly.

Furthermore, external factors such as smoking and alcohol intake have been investigated in relation to DISH. The five studies investigating smoking and DISH show contradicting results [4,28,29,35,39]. Significant differences were found by Kagotani et al. with more current regular smokers in the DISH group (21.1%) compared with the non-DISH group (11.9%) [28]. In contrast, two studies described a significantly lower percentage of current smokers in the DISH group (3.3–57.7%) compared with the control group (7.2–65.9%) [29,35]. Regular alcohol consumption had no relation to the presence of DISH in two studies after correcting for confounders [28,35].

Role of the anterior longitudinal spinal ligament

In literature, DISH is often regarded as the ossification of the anterior longitudinal ligament (ALL); however, data to support this theory are lacking [19]. Macroscopic research on cadaveric spines with DISH showed that the ALL was still present in the midline at levels without new bone formation and showed displacement of ALL to the contralateral side at levels where new bone had formed [49]. Thus, DISH may not originate from the ALL and further research on a microscopic level is needed.

Genetics

A genetic predisposition for the development of DISH was described in different affected families with DISH [50,51]. In dogs, the boxer breed has been shown to have a significantly higher prevalence of DISH (40%) compared to all other dogs (4%) [52,53]. Furthermore, a mouse model lacking equilibrative nucleoside transporter 1 was discovered mimicking DISH [54]. Single nucleotide polymorphisms in the COL6A1 and FGF2 genes were related to the presence of DISH in preliminary studies [19,55,56]. Future work should focus on genetics, using genome-wide association studies (GWAS), to find associations between single nucleotide polymorphisms and the presence of DISH.

Vascular factors

Radiological and anatomical research on subjects with DISH has shown that new bone forms anterolaterally of the spine, most frequently occurring in the lower thoracic spine (Th9 – Th11) [10,57–59]. The location of the newly deposited bone is away from pulsating large vessels such as the

aorta, explaining the asymmetrical location in the thoracic spine and symmetrical distribution in the cervical spine [49,60,61]. In patients with situs inversus (a congenital condition in which left/right organs are reversed), the newly formed bone has been shown to be located on the contralateral left side [62,63]. Furthermore, the flowing character of the new bone formation is suggested to be the result of segmental vessels, crossing at the mid-vertebral level, and again in the cervical spine the lack of segmental vessels results in less flowing bone formation [49,60,61]. Vascular factors are thus likely involved in the pathogenesis of DISH. In a study by El Miedany et al., a significant increase in the number and width of nutrient foramina of the vertebral body and hypervascularity was observed in subjects with DISH [64]. However, it remains unknown what is the cause and what is the effect; did the newly formed bone request more afferent blood vessels, or did the increase in blood vessels facilitate or result in the formation of new bone.

Metabolic and molecular factors

The relation between DISH and (components of) the metabolic syndrome is evident [31,35]. Hypothetically, this association is the result of extra available "energy," which is needed for the formation of new bone, explaining the elevated prevalence of DISH in obese patients or the lack of DISH in nonobese patients. This theory, however, does not explain why only new bone is formed and in such a specific location as the spine. In subjects with obesity, a higher ratio of visceral to subcutaneous fat also appears to be relevant because it is correlated with a higher ratio of proinflammatory to anti-inflammatory plasma cytokine levels, suggestive of a chronic elevated inflammatory response [65,66]. Growth hormone and insulin-like growth factor 1 promote bone formation and were found to be increased in subjects with DISH [19]. Furthermore, signaling pathways such as Wnt, NFκB, BMP2, PGI2, and endothelin 1 have all been suggested as potential elements promoting bone formation in DISH [19]. These potential contributing factors require more in-depth research, as the pathway that leads to new bone formation is still unclear.

Clinical relevance

The diagnosis of DISH is often overlooked by clinicians. This could be the result of a lack of knowledge or because of the variation of clinical symptoms related to DISH. However, diagnosing the presence of DISH is of clinical importance, because associations with the metabolic syndrome, coronary and aortic disease, and respiratory effects are strong.

Pain and functional impairment

Many individuals with DISH are asymptomatic, resulting in DISH often being discovered as a coincidental finding during radiological examination for other conditions [2,19,67,68]. Yet, various clinical symptoms have been reported in patients with DISH. First of all, back pain and spinal stiffness are reported as a general symptom of DISH [19]. In a cohort of 200 patients with DISH, 72% of patients reported back pain and 84% of patients reported spinal stiffness [69]. However, data are conflicting, when comparing subjects with and without DISH, Schlapbach et al. did not find any statistical differences between groups regarding back pain [70]. In fact, spinal hyperostosis might also be protective for back pain, according to a study by Holton et al., showing less back pain in patients with DISH compared to controls [4]. Authors suggested that DISH increases the stability of the spine and thereby limits pain, as a result of the naturally occurring fusion. In subjects with DISH, bending was reported as difficult in 19.8%, which was significantly more frequent compared with subjects without DISH (9.8%, $p < 0.0001$, after adjusting for age, sex, weight, stroke, arthritis, exercise, and Cobb angle $p = 0.02$) [29]. Grip strength was also significantly lower in the DISH group (17.9 kg) when compared with the group without DISH (19.9 kg and $p < 0.001$, adjusted $p = 0.01$) [29]. The authors of this large cross-sectional study ($n = 1591$) concluded that people with DISH are more likely to experience physical functional impairment. Longitudinal research should be conducted to investigate if patients with DISH have more back pain in the early stage compared to the more matured stage of DISH. Furthermore, back pain and

the progression of DISH should be researched in relation to spinal flexibility to support the theory by Holton et al. [4].

In case of peripheral manifestations of DISH, symptoms of pain, decreased range of motion, and stiffness of affected joints have been described [3,71]. Hyperostosis in extraspinal locations is usually observed symmetrically and can coexist with osteoarthritis, although DISH also affects joints not typically known to display osteoarthritis, such as the elbows and ankles [19]. Nevertheless, comparing matched cases with and without DISH, pain and stiffness in joints was reported less in the DISH group [40]. The small number of matched cases (n = 59) or inadequate matching could explain these results and larger studies should be performed to better investigate the relation between DISH and extraspinal symptoms.

Dysphagia and airway obstruction

As a result of the abundant bone located anterior to the vertebral bodies in the cervical spine, the trachea and esophagus can be displaced, leading to dysphagia and airway obstruction [72]. Multiple case reports are available in the literature describing this clinical manifestation of cervical DISH with the terms “unexpected” or “rare” in their titles. However, in a systematic review that included articles describing patients with symptoms of cervical DISH, at least 200 of such patients were described between 1980 and 2009 [72]. DISH might be a more important contributor to these symptoms than previously thought, and physicians should consider the presence of cervical hyperostosis if patients present with dysphagia or airway obstruction not readily explained by other causes. The treatment options for symptomatic cervical DISH are conservative or surgical. The operative removal of the abundant bone immediately relieves mechanical pressure on surrounding tissues, although the reoccurrence of bone growth years after initial surgical resection has been described [73–75].

Spinal fractures

For trauma patients, the most important consequence of an ankylosed spine as a result of DISH is the elevated fracture risk of the spine [76]. Fractures are four times more common in the ankylosed spine compared to the nonankylosed spine and have a high risk of up to 58% of associated spinal cord injury [59,77–83]. The increased fracture risk is the product of the stiff spine that acts similar to a long bone following trauma. In the healthy, nonankylosed spine, energy can be distributed over multiple mobile segments, including intervertebral discs, apophyseal joints, and their surrounding ligaments, joint capsules, and muscles [84]. By contrast, the ankylosed spine does not have the appropriate capability to dissipate energy after a traumatic event, making it more prone to unstable/displaced fracture types [85,86]. In the ankylosed spine, hyperextension (AOSpine-B3) and displacement (AOSpine-C) type fractures are the most frequently observed fracture patterns [85,87,88]. Typically, fractures in DISH pass through the vertebral body, because the abundant cortical bone completely bridges the intervertebral disc, leaving the mid-section of the vertebral body as the weakest point [20,60,84,89]. Spinal fractures in DISH are associated with greater instability, a higher risk of spinal cord injury, and more complications [59,77,90]. Early recognition of a spinal fracture in a patient with DISH is essential to avoid further displacement of the spinal column and spinal cord injury [91]. Unfortunately, a delay in diagnosis is reported in 19%–41% of ankylotic spine fractures. Initial neurological function deteriorated in 81% (17/21) of patients with delayed diagnosis compared to 5% (3/63) of patients with timely diagnosis [77,80]. Three factors contribute to the delay in diagnosis and potential deterioration of neurological status: minimal trauma upon presentation that elicits no more than a low clinical index of suspicion, no clear exacerbation in the severity of chronic back pain (present in over 50% of the elderly with and without DISH), and no increased level of suspicion with subtle abnormalities on imaging. In patients with DISH, conventional radiography may be difficult to interpret, because of morphological changes in the ankylosed spine and the presence of DISH ossifications within the field of view that can hamper the identification of traumatic injury [85]. CT and a low threshold additional MRI are recommended to evaluate both osseous and ligamentous injuries in patients with DISH [92,93]. The treatment strategy for a fracture of an ankylosed spine may be nonsurgical or surgical. Based on the data of two large retrospective studies, patients with a fracture of the ankylosed spine had a significantly improved chance of

survival if the fracture was surgically stabilized, although a selection bias was likely present [77,79,88]. If the treating surgeon decides to perform surgery, several considerations should be kept in mind. The intubation process could be compromised by the stiff and deformed cervical ankylosed spine, positioning/manipulation of the patient should be performed with utmost care and posterior stabilization is currently the preferred method with fixation of at least three levels above and three levels below the fracture. Compared with percutaneous pedicle screw fixation techniques, open stabilization is associated with more complications, longer hospital stay, more blood loss, and a higher mortality rate in several small retrospective studies [94,95]. Percutaneous pedicle screw-based fixation techniques are therefore the favored method for thoracolumbar B3 or C type fractures without neurological deficit [96–98]. Physicians' awareness regarding implications of spinal ankylosis is essential for the adequate diagnosis and treatment of patients with a fractured ankylosed spine.

Treatment

Because of the lack of knowledge on the pathogenesis of DISH, direct treatment for this condition is currently unavailable. Only symptomatic therapy has been suggested in the literature [19]. Analgesics and NSAIDs can be used for pain from axial or peripheral manifestations of DISH. In case of metabolic disarrangement, standard care for the metabolic syndrome should be given [99]. Surgical interventions might be required in cases of severe symptomatic cervical DISH and for unstable spinal fractures [76].

Conclusions

DISH is a common systemic disorder characterized by ectopic mature bone formation. The prevalence of DISH is expected to rise as it is related to older age and the metabolic syndrome. DISH can nowadays be reliably diagnosed by radiography and CT. The clinical relevance is increasing beyond the trauma setting to a likely involvement of the cardiovascular, respiratory, and gastroenteral system. Unravelling the etiology can not only help in resolving medical issues related to DISH, but it can also impact the field of regenerative medicine, as fine-tuning of local and systemic bone formation is of great medical relevance.

Practice points

- DISH is a bone-forming disease with unknown pathophysiology
- DISH is associated with older age, male sex, metabolic syndrome, and atherosclerosis
- Diagnosing the presence of DISH is of clinical importance

Research agenda

- Research in the early stage of DISH is needed to understand the etiology of DISH.
- Unravelling the pathogenesis of DISH can impact the field of regenerative medicine and bone tissue regeneration.

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Declaration of Competing Interest

All authors have no conflicts of interest to report.

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