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Review Article

Diffuse idiopathic skeletal hyperostosis: A review of current literature

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Abstract

Diffuse Idiopathic Skeletal Hyperostosis (DISH) is a non-inflammatory skeletal disease characterized by exuberant ossification at entheses, particularly affecting the anterior longitudinal ligament of the spine and multiple peripheral sites. This review synthesizes current literature on the epidemiology, pathogenesis, clinical spectrum, diagnostic criteria, and management strategies for DISH. Epidemiological data indicate a prevalence of approximately 12% in the general population, increasing with age and exhibiting a male predominance, although metabolic comorbidities may modify sex-related risk. The pathophysiology remains incompletely defined but implicates metabolic syndrome components, growth factor dysregulation, genetic predisposition, and local vascular alterations in aberrant bone formation. Clinically, DISH ranges from asymptomatic radiographic findings to severe manifestations including back pain, stiffness, dysphagia, respiratory compromise, neurological deficits, and increased fracture risk. Radiographs remain the primary diagnostic modality, supplemented by CT and MRI for early detection and differential diagnosis from conditions such as ankylosing spondylitis. Management focuses on symptom relief through pharmacologic agents, physical therapy, and lifestyle modifications, with surgery reserved for complications like dysphagia or unstable fractures. Significant gaps persist regarding early disease biomarkers, mechanistic pathways, and targeted therapies. Future research should emphasize longitudinal studies, molecular investigations, and randomized trials to inform evidence-based interventions. By consolidating findings on genetic loci such as RUNX2, BMP, and Wnt pathway genes, this review highlights potential molecular targets. Additionally, it underscores the importance of integrated care addressing metabolic syndrome features. Emerging technologies, such as 'clinical trials in a dish', offer promise for personalized treatment development, refine therapies.

Keywords: DISH, Enthesopathy, Metabolic syndrome, Osteogenesis, Imaging, Management

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1. Introduction

Diffuse Idiopathic Skeletal Hyperostosis (DISH), also recognized as Forestier's disease, represents a systemic, non-inflammatory condition characterized by the excessive formation of new bone (ossification and calcification) primarily within the axial and peripheral skeleton.[1] This pathological process specifically targets ligaments, tendons, and fasciae at their points of attachment to bone, known as entheses.[1] The hallmark pathological feature of DISH is the ossification of the Anterior Longitudinal Ligament (ALL) along the vertebral column, with the thoracic spine, particularly segments T7-T11, being the most frequently affected region.[3]

The formal terminology "Diffuse Idiopathic Skeletal Hyperostosis" was introduced by Resnick and colleagues in 1975. This naming convention marked a significant advancement in the understanding of the condition, moving beyond its initial focus on isolated spinal involvement to encompass its widespread extraspinal manifestations.[2] Historically, the condition was first described by Forestier and Rotes-Querol in 1950 as "senile ankylosing vertebral hyperostosis".[13] The subsequent evolution of its nomenclature, from "senile ankylosing vertebral hyperostosis" to "ankylosing spinal hyperostosis" and ultimately to "Diffuse Idiopathic Skeletal Hyperostosis," reflects a broadening recognition of the disease's systemic nature and its occurrence in individuals beyond the elderly population, as well as its impact beyond the spine.[2] This shift in terminology is not merely a semantic change; it underscores a fundamental progression in medical knowledge. Early characterizations were incomplete, focusing predominantly on spinal changes and an older demographic. However, subsequent research revealed that DISH is a more pervasive, systemic condition affecting various entheseal sites throughout the body, including peripheral joints such as the pelvis, patella, calcaneus, and

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olecranon.[2] This expanded understanding necessitates a broader diagnostic perspective, moving beyond isolated spinal findings to a holistic assessment of the entire musculoskeletal system.

Despite the extensive skeletal changes characteristic of DISH, the condition frequently presents asymptomatically and is often discovered incidentally during imaging studies performed for unrelated medical reasons.[3] However, when symptoms do manifest, they can range from mild musculoskeletal pain and stiffness to severe complications. These complications may include gastrointestinal issues (e.g., dysphagia, odynophagia, reflux, pharyngeal perforation, weight loss), respiratory distress (e.g., hoarseness, cough, sleep apnea, laryngeal stridor), cardiovascular conditions, and neurological impairments (e.g., spinal cord compression, muscle weakness, numbness, tingling, sensory loss, Horner's Syndrome, aphonia) due to direct bone compression of adjacent structures.[3]

2. Global Prevalence and Epidemiology

DISH is a relatively common condition, although reported prevalence rates exhibit considerable variability across different studies, ranging from 2.5% to 37% in the general population.[1] This wide range is partially attributable to inconsistencies in the diagnostic criteria applied and the specific anatomical locations of structural manifestations assessed in various research endeavors.[3] A recent systematic review and meta-analysis provided more consolidated estimates, reporting an overall prevalence of approximately 11.92% (95% CI, 8.68%-15.59%) in the general population and 14.30% (95% CI, 10.10%-19.09%) in clinical patient cohorts.[16]

2.1. Age-related prevalence

The prevalence of DISH consistently increases with advancing age, primarily affecting adults older than 45 years and becoming significantly more prominent in individuals in their 60s and 70s.[1] The condition is rarely reported in patients aged 50 or younger.[10] Current theories suggest that the underlying pathological process may commence between the third and fifth decades of life, with clinical symptoms typically manifesting much later.[10]

2.2. Sex disparity

A consistent male preponderance is observed in DISH, with overall prevalence rates significantly higher in men (17.87% in population-based studies, 18.73% in clinic-based studies) compared to women (6.49% in population-based, 10.16% in clinic-based studies).[1] However, one study noted that when controlling for diabetes mellitus (DM) and congestive heart failure (CHF), female sex was identified as a major predictor, with women being approximately 3.6 times more likely to develop DISH.[17] This finding warrants closer examination. While raw prevalence data consistently show more men affected, this particular analysis suggests that the underlying mechanisms or risk factors might interact differently between sexes. If women with DISH are more likely to present with significant metabolic comorbidities, such as diabetes and congestive heart failure, and these comorbidities are strong drivers of DISH pathogenesis, then the observed male predominance in overall prevalence might be influenced by other factors, such as occupational exposures, lifestyle differences, or perhaps a higher clinical threshold for diagnosis in women. The implication is that for women, the presence of DISH might be a more potent indicator of underlying metabolic derangement, suggesting a more complex interplay between sex and metabolic health. This highlights the need for more sophisticated epidemiological studies employing multivariate analyses to disentangle these complex relationships, potentially leading to gender-specific approaches for risk assessment and early detection.

2.3. Geographical and racial/ethnic variations

Prevalence estimates also vary by continent and race/ethnicity. Population-based studies indicate the highest prevalence in Oceania (30.07%), followed by North America (13.46%), Europe (11.16%), and Asia (10.07%).[16] In clinic-based studies, Asia (16.32%) and Europe (13.20%) show higher rates, while Africa reports the lowest (3.93%).[16] Racial differences in prevalence have also been reported, with White (11.90%) and Asian (10.07%) populations generally showing higher rates than Black populations (8.77%) in population-based studies.[16]

3. Etiology and Pathophysiology

The precise etiology of DISH remains largely unknown, and its pathogenesis is considered multifactorial, involving a complex interplay of genetic, metabolic, endocrinologic, anatomic, environmental, and potentially toxic factors.[1] It is broadly characterized as a non-inflammatory condition driven by an underlying metabolic derangement that results in new bone formation.[1]

3.1. Metabolic disorders

A robust and consistent association exists between DISH and various components of metabolic syndrome. These include obesity, type 2 diabetes mellitus (DM), hyperinsulinemia, dyslipidemia, and hyperuricemia.[1] Patients diagnosed with DISH frequently exhibit higher body mass index and elevated serum uric acid levels.[9] The link between obesity and a sedentary lifestyle is often cited as a significant contributing factor to the development of these metabolic comorbidities.[3] The consistent and strong association between DISH and these metabolic syndrome components suggests that DISH might not merely be a musculoskeletal manifestation but rather a skeletal indicator or complication of systemic metabolic dysregulation. This implies that the presence of DISH could serve as a clinical flag for underlying metabolic issues, and, conversely, effective management of these metabolic comorbidities could be a crucial, albeit indirect, strategy for influencing DISH progression or symptom

severity, even if a direct causal link is not yet fully elucidated. This perspective shifts DISH from being a purely localized orthopedic problem to a systemic disease with skeletal manifestations, broadening the scope of its clinical management.

3.2. Hormones and growth factors

Excess levels of various growth factors are hypothesized to stimulate the transformation of mesenchymal cells into fibroblasts and osteoblasts, thereby promoting new bone formation.[1] Key implicated factors include insulin, insulin-like growth factor 1 (IGF-1), and transforming growth factor-β1.[1] High circulating levels of insulin and growth hormone in DISH patients are thought to contribute to osteoblast cell growth and proliferation.[9] The mechanism involves these factors acting on fibroblasts, chondrocytes, and collagen fibers of cartilage to promote bone regeneration.[16]

3.3. Vascular changes

Pathological studies have revealed a significant increase in the number and width of nutrient foramina in affected ligaments and vertebrae, indicative of hypervascularity.[9] This observation suggests that a localized vascular disorder may play a role in the pathogenesis of DISH, potentially acting as a localizing factor for the ossification process.[9] Furthermore, atherosclerosis, a condition often linked to hyperlipidemia and diabetes, can lead to endothelial damage and the aggregation of platelet-derived growth factor (PDGF), which subsequently promotes osteoblast proliferation.[9] This connection highlights how systemic metabolic issues can directly influence local bone formation through vascular pathways.

3.4. Genetic factors

While studies on human leukocyte antigen (HLA) factors have yielded conflicting results regarding a definitive genetic link [9], a genetic predisposition is suspected to contribute to DISH susceptibility.[3] Recent genetic association analyses have identified 10 DISH-related loci, including genes involved in bone remodeling such as RUNX2, BMP signaling pathway genes (e.g., CHRDL2, NOG, GDFS), and Wnt signaling pathway genes (ROR2).[16] (**Table 1**). These findings collectively imply a significant role for overactive osteogenesis in the development of DISH.[16] Notably, HLA-B8 is commonly found in both DISH and diabetes mellitus patients, suggesting a potential shared genetic susceptibility or a more complex interaction between genetic predisposition and metabolic health.[10]

3.5. Other factors

Elevated serum levels of retinol and retinol-binding protein (related to Vitamin A) have been observed in DISH patients, suggesting a potential role for vitamin A in the development of ossification, particularly of the posterior longitudinal ligament (OPLL), which is frequently associated with DISH.[4] Mechanical stress on posterior ligaments has also been suggested as an important factor in the progression of OPLL, with uniaxial cyclic stretching enhancing osteogenic differentiation in spinal ligament cells.[9]

4. Clinical Manifestations

DISH is characterized by a spectrum of clinical presentations, ranging from completely asymptomatic to severely debilitating, depending on the location and extent of ossification.[3]

Table 1: Genetic loci associated with DISH

Locus (Gene)	Chromosomal Location	Associated Pathway / Role
RUNX2	6p21	Master regulator of osteoblast differentiation; controls transcription of bone matrix proteins and osteogenic genes.
CHRDL2	16p13	Encodes chordin-like 2, a BMP antagonist; modulates BMP signaling balance and osteogenic differentiation.
NOG	17q22	Encodes noggin, a secreted BMP antagonist; regulates bone morphogenetic protein activity and prevents excessive osteogenesis.
GDF5	20q11	Growth differentiation factor 5; member of the BMP family, promotes chondrogenesis and osteoblast maturation.
ROR2	9q22	Receptor tyrosine kinase-like orphan receptor 2; transduces noncanonical Wnt signals to stimulate osteoblast proliferation and matrix deposition.
IL11	19q13	Interleukin 11 cytokine; involved in osteoclast-osteoblast coupling, promotes bone formation in response to inflammatory signals.
COL6A1	21q22	Collagen type VI alpha 1 chain; extracellular matrix protein—variants linked to aberrant ligament ossification in Japanese cohorts.

4.1. Asymptomatic and symptomatic presentations

In a significant number of cases, DISH is discovered incidentally during imaging studies performed for other medical reasons, with patients remaining entirely asymptomatic. [3] This often leads to a discrepancy between the extensive radiographic findings and the minimal clinical symptoms.[10] When symptoms do occur, they are typically attributed to altered biomechanics of the axial skeleton, direct compression of adjacent structures by bony growths, or nerve impingement.[3] The classic symptomatic presentation often involves an older patient experiencing increasing back pain and stiffness, particularly in the morning.[3] The axial skeleton is the most commonly affected site, with the thoracic spine (T7-T11) being the primary region of involvement. [3] Beyond spinal pain and stiffness, a wide array of symptoms can manifest:

1. Musculoskeletal: Decreased range of motion (ROM) in the axial skeleton or peripheral joints, polyarticular pain, acute monoarticular synovitis, and pain at peripheral entheseal sites.[3] Peripheral enthesopathy can occur in shoulders, elbows, knees, or calcaneus, with foot and ankle involvement reported in up to 70% of patients, often presenting as heel spurs, Achilles tendinitis, and plantar fasciitis.[10] Hypertrophic changes in peripheral joints are often more pronounced than in primary osteoarthritis, and joints typically unaffected by primary osteoarthritis (e.g., hip, knee, shoulder, elbow, metacarpophalangeal joints) are commonly involved.[3]
2. Gastrointestinal: Dysphagia (difficulty swallowing), odynophagia (painful swallowing), hoarseness, cough, weight loss, reflux, and pharyngeal perforation can result from osteophyte compression in the cervical spine. [3] Severe dysphagia can progress to an inability to ingest liquids.[22]
3. Respiratory: Airway obstruction, laryngeal stridor, dyspnea, and sleep apnea can also arise from cervical osteophyte impingement.[3] Involvement of sternocostal and costochondral junctions may lead to restrictive lung disease due to limited thoracic cage expansion.[12]
4. Neurological: While typically uncommon, neurological impairments can manifest as spinal cord compression, muscle weakness, numbness, tingling, sensory loss, dysphonia, Horner's Syndrome, and aphonia.[3] Myelopathy can result from direct cord compression, especially when associated with ossification of the posterior longitudinal ligament (OPLL).[15]
5. Fracture Risk: Patients with DISH have an increased risk of unstable spine fractures, even after minor trauma, due to the ankylosed nature of the spine, which behaves like a long bone and creates longer "lever arms" that concentrate mechanical stress.[4] This increased vulnerability to fracture is a significant clinical concern.

4.2. Systemic associations and comorbidities

DISH is strongly associated with various systemic conditions and metabolic dysfunctions, particularly metabolic syndrome.[1] These associations are so prevalent that DISH is often considered a skeletal indicator of underlying metabolic derangement.[1] Commonly associated comorbidities include:

1. Metabolic Syndrome Components: Diabetes Mellitus (Type 2 DM), obesity, hyperinsulinemia, dyslipidemia, and hyperuricemia.[1] A majority of metabolic syndromes associated with DISH are linked to obesity and a sedentary lifestyle.[3]
2. Cardiovascular Conditions: Hypertension, atrial fibrillation, left ventricular hypertrophy, peripheral arterial disease, and a general increased risk of cardiovascular disease.[3] Some studies have shown a higher risk of cardiac events, cardiac atherosclerosis, and coronary artery disease in DISH patients.[17]
3. Other Associations: Osteoarthritis, [3] gout,[10] dementia,[17] chronic obstructive pulmonary disease (COPD),[17] and peripheral vascular disease (PVD).[17] The association with dementia, while not extensively discussed in prior literature, aligns with the older age of the DISH cohort.[17]

It is important to note that while these systemic conditions are frequently associated with DISH, a formal diagnosis of DISH does not mandate their presence.[3] However, their high prevalence underscores the importance of a multidisciplinary approach to patient management, addressing both the musculoskeletal manifestations of DISH and its systemic comorbidities.[3]

5. Diagnosis and Differential Diagnosis

5.1. Universally accepted diagnostic criteria and their limitations

The diagnosis of DISH primarily relies on radiographic criteria established by Resnick and Niwayama in 1976.[1] These criteria are widely used and encompass:

1. Flowing ossifications along the anterolateral aspect of the spine, involving at least four contiguous vertebral levels (or three consecutive vertebral levels in some interpretations).[1]
2. Preservation of intervertebral disc spaces without extensive degenerative intervertebral disease.[1]
3. Absence of apophyseal (facet) joint degeneration or bony ankylosis, and no sacroiliac (SI) joint erosion, sclerosis, or fusion.[1]

A significant limitation of the Resnick and Niwayama criteria is that they primarily apply to end-stage disease, where the spine is already ankylotic.[1] This means that early-phase DISH, which is marked by new involvement of previously unaffected motion segments and localized nodules of ectopic mineralization, may not meet these stringent criteria, potentially delaying diagnosis.[2] Some researchers,

like Ustinger, have suggested lowering the threshold to three contiguous vertebrae and adding the presence of pelvic enthesophytes to facilitate earlier diagnosis, though these alternative criteria have not gained widespread acceptance.[1] Consensus and definitive literature support for diagnostic elements beyond exuberant new bone formation and enlarged bony bridges in characteristic spinal locations remain limited.[10]

5.2. Imaging modalities and features

Imaging plays a central role in the diagnosis and characterization of DISH.

1. Radiographs: Plain radiographs are the primary modality for initial diagnosis, famously revealing the "flowing candle wax" appearance along the anterolateral aspect of the spine.[8] This refers to non-marginal syndesmophytes projecting horizontally from the vertebrae, leading to extra-articular ankylosis.[10] Other radiographic features include a bumpy contour, subjacent radiolucency, and irregular bony excrescences at vertebral margins.[29]
2. Computed Tomography (CT) Scans: CT scans offer a more detailed view of the ossification patterns and are particularly useful for confirming the extent of anterior ossification and assessing impingement on adjacent structures.[15] CT can also detect early-phase DISH, characterized by localized nodules of ectopic mineralization external to and within the intervertebral disc.[20] These nodules, often described as 'nodular soft-tissue calcification,' are more abundant in early stages and may either be resorbed or integrated into ectopic bridges over time.[28] CT has also shown a higher prevalence rate of DISH compared to radiographs alone.[10]
3. Magnetic Resonance Imaging (MRI): MRI is increasingly suggested, especially for symptomatic, painful, or post-traumatized DISH patients, as it can aid in differentiating DISH from other conditions when other modalities are inconclusive.[26] MRI can also reveal early changes in sacroiliac joints, which is crucial for differential diagnosis.[18]

Extraspinal features on imaging commonly include hyperostosis at ligament attachments in the pelvis (iliac crest, ischial tuberosity, greater trochanters), calcaneus (heel spurs, Achilles tendinitis, plantar fasciitis), tarsal bones, ulnar olecranon, and patella.[2]

5.3. Differentiation from other spinal disorders, particularly ankylosing spondylitis (AS)

Differentiating DISH from other spinal disorders, especially Ankylosing Spondylitis (AS) and other seronegative spondyloarthropathies (SpA), is crucial due to overlapping clinical symptoms and radiographic findings.[1] Both DISH and SpA are bone-producing diseases involving the axial and appendicular skeletons, with enthesopathy being a major feature in both.[1] However, key distinctions exist:

1. Pathogenesis: DISH is considered a non-inflammatory condition with an underlying metabolic derangement, whereas AS is an inflammatory disease.[1] While local inflammation may play a role in DISH development, it is fundamentally different from the systemic inflammation seen in AS.[1]
2. Age of Onset: DISH typically affects older individuals (over 45-50 years), with prevalence increasing significantly with age.[1] AS, in contrast, usually presents in younger adults (15-30 years old).[6]
3. Sacroiliac (SI) Joints: A primary distinguishing feature is the preservation of SI joint spaces and absence of erosion, sclerosis, or fusion in DISH.[1] AS, however, is characterized by bilateral and symmetric sacroiliitis, often leading to joint fusion.[6] While SI osteophytes have been observed in DISH patients, true erosions are absent.[10]
4. Apophyseal Joints: DISH typically shows absence of apophyseal joint obliteration, unlike AS where ankylosis of these joints is common.[1]
5. Spinal Ossification Pattern:
6. DISH: Characterized by thick, prominent "flowing" ossifications along the anterolateral aspect of the spine, resembling "dripping candle wax".[10] These osteophytes are primarily horizontal in nature and often located on the right side of the thoracic spine.[1] The intervertebral disc spaces are preserved.[1]
7. AS: Presents with slender, vertical syndesmophytes that involve the outer margin of the annulus fibrosus, leading to a "bamboo spine" appearance.[6] Vertebral bodies may become squared, and disc spaces can show degenerative changes.[6] Syndesmophytes in AS are vertically oriented with no predilection to any side.[1]
8. Genetic Predisposition: AS has a strong association with HLA-B27, which is typically absent in DISH.[8]
9. Clinical Severity: DISH is generally considered a milder condition compared to AS and may even present without pain, whereas AS typically causes inflammatory back pain and stiffness.[6]

Despite these clear distinctions, differentiating the two can be challenging, especially in advanced stages where both conditions can produce new bone formation and affect tendons, ligaments, and entheses.[18] Coexistence of DISH and AS has also been described in several case studies. [1] Clinical suspicion combined with advanced imaging techniques (X-rays, CT, MRI) and a thorough understanding of the unique features of each condition is essential for accurate diagnosis and appropriate management.[18]

6. Management Strategies

Given the lack of disease-modifying therapeutics, the management of DISH is primarily directed towards symptom

management, addressing associated metabolic and constitutional comorbidities, and treating any arising complications.[3]

6.1. Conservative management

Conservative approaches are typically the first line of treatment for patients without unstable spine fractures or neurological deficits.[31]

1. Pharmacological Interventions
    a. Pain Relievers and Anti-inflammatories: Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics like acetaminophen are commonly used to manage pain and stiffness.[3] Muscle relaxants and sedation may also be employed.[3] While these can be helpful, their benefits are often modest and may be limited by toxicity.[30]
    b. Bisphosphonates: These medications are mentioned as a treatment option, though their specific efficacy for DISH-related ossification is not extensively detailed.[10]
    c. Corticosteroid Injections: May be an option for severe pain refractory to exercise and physical therapy, with the goal of facilitating a return to physical activity.[4]
    d. TNF Inhibitors (TNFi): An observational study found that TNFi (e.g., Etanercept, Adalimumab, Golimumab, Certolizumab) were efficacious in the majority of patients with clinically active DISH, leading to sustained reductions in BASDAI scores similar to those observed in Spondyloarthritis (SpA) patients.[30] Unequivocal regression of DISH was observed in some responders after four years. This finding challenges the dogma that DISH is uniformly non-inflammatory and suggests a potential inflammatory component in some patients, warranting further investigation through randomized controlled trials.[30]
2. Physical therapy and lifestyle modifications
    a. Exercise and Physical Therapy: Considered essential for controlling back pain, improving stiffness, and enhancing range of motion.[3] Swimming is particularly beneficial as it provides a full-body workout with reduced injury risk.[4] Physical therapy can help increase mobility, provide pain relief, aid in weight reduction, and offer joint protection and falls prevention strategies.[3]
    b. Heat Therapy: Can help relieve early-morning pain and stiffness.[4]
    c. Weight and Blood Sugar Control: Given the strong association between DISH and obesity and diabetes, maintaining a healthy weight and blood sugar is crucial. Treating these metabolic conditions is considered the closest approach to a "cure" for DISH.[3] Dietary modifications, including fluids and soft foods, may be necessary for patients with dysphagia.[3]
    d. Orthotics: Special shoe inserts may improve walking for patients with heel spurs.[4]
    e. Orthosis Immobilization: Bracing can improve symptoms like back pain and stiffness, though patient compliance is a strong predictor of clinical outcomes.[31] For extension-type DISH fractures without neurological deficits, external orthosis alone has shown a high success rate (95.5%) in select patients who are not surgical candidates, but noncompliance carries a risk of neurological injury.[32]

6.2. Surgical interventions

Surgical intervention is generally reserved for severe complications or when conservative measures fail, particularly for debilitating symptoms such as severe dysphagia, airway obstruction, or unstable spinal fractures with or without neurological deficits.[3]

6.2.1. Peri-operative considerations

Patients with DISH often have significant comorbidities (e.g., cardiovascular disease, obesity, type 2 diabetes, metabolic syndrome), classifying them as higher anesthetic risk (ASA 2 or higher).[22] Pre-operative nutritional support is vital for dysphagic patients to improve wound healing and reduce infection risk.[22] Airway management can be challenging due to cervical osteophytes, potentially requiring emergency tracheotomy.[22] Close collaboration between neurosurgery, orthopedic surgery, and otolaryngology specialists is recommended for comprehensive planning and management.[22] Careful patient positioning is mandatory to avoid complications, especially with the stiff, ankylosed spine.[22] Intraoperative imaging, such as fluoroscopy, is crucial for visualization and preventing damage to vertebral bodies and disc spaces.[22]

6.3. Operative techniques and indications

1. Cervical Osteophytectomy for Dysphagia/Airway Obstruction: Surgical removal of symptomatic cervical osteophytes is highly effective, with success rates for dysphagia improvement around 95.5%.[22] Approaches include the open anterolateral approach (Smith-Robinson), which is preferred for ease of osteophyte removal and extended exposure.[22] Curved chisels have been associated with shorter operation times compared to high-speed burrs.[22] It is critical to preserve the annulus fibrosus to maintain disc integrity and differentiate between vascular vertebral bone and avascular osteophyte overgrowth to minimize bleeding.[22] Some authors recommend early surgery for mild dysphagia due to the progressive nature of DISH.[22] Recurrence of dysphagia due to osteophyte regrowth is estimated at 1.7% after a mean follow-up of 3.7 years.[22]
2. Spinal Fractures: Surgical treatment aims to stabilize the spine and prevent or mitigate neurological damage.[22]

DISH-related fractures are often highly unstable due to the "long lever arm" effect of the fused spine.[10]

a. Posterior Approach: The most common approach for trauma surgery in DISH, providing multiple fixation points and exposure for decompression.[22]
b. Anterior Approach: Limited evidence and associated with higher complication rates and implant failure in DISH patients with vertebral fractures. [22]
c. Combined Anterior and Posterior Approach: Recommended for unstable B- and C-type cervical fractures, providing greater stability, though the less invasive posterior approach may be preferred due to similar outcomes and fewer complications. [22]
d. Minimally Invasive Posterior Approach: A viable alternative for neurologically stable patients, offering improved perioperative outcomes, less blood loss, and shorter operative times. [22]
e. Outcomes: Fusion rates are generally high (87% to 100%), but reoperation rates range from 0 to 14%, mainly for debridement after infection or refixation after implant failure. [22] DISH is a significant risk factor for further surgery due to pseudoarthrosis or adjacent segment disease (ASD) after lumbar interbody fusion (LIF).[25] The high mechanical stress on segments free of ossification distal to L-DISH can induce disc degeneration or ligamentum flavum hypertrophy, leading to a need for further surgery for lumbar spinal stenosis (LSS).[25]

6.3.1. Post-operative care

For dysphagia, diet progression from liquids to solids is gradual, and monitoring for hematoma formation is crucial.[22] For fractures, early mobilization is important for rehabilitation.[22] Spinal cord injury (SCI) rehabilitation is critical for recovery, often a long process with potential complications. [22]

7. Long-Term Prognosis and Complications

DISH is a progressive condition, with intervertebral ossification advancing with age.[10] The continuum of DISH is characterized by distinct features at different phases, from early involvement of previously unaffected motion segments to complete bridging over several years.[28]

7.1. Progressive nature and fracture risk

The ossification process in DISH progresses over time, leading to decreased mobility in affected regions until complete ankylosis occurs.[10] This progressive stiffening of the spine renders it more vulnerable to trauma, even from relatively low-energy impacts.[12] The fused spinal segments behave like long bones, creating "longer lever arms" that concentrate mechanical stress at unfused segments or fracture sites, leading to severely displaced and unstable spinal fractures.[4] The mortality rate for patients with DISH-related fractures can be as high as 38.1%.[24] Delayed diagnosis of spinal fractures is common, especially when neurological deficits are initially absent.[11] Furthermore, DISH is a significant risk factor for pseudoarthrosis or adjacent segment disease (ASD) and the need for further surgery following short-segment lumbar interbody fusion.[25]

7.2. Specific complications and their impact on mortality

Beyond musculoskeletal issues, DISH can lead to severe and life-threatening complications:

1. Dysphagia and Airway Obstruction: As discussed, bony growths in the cervical spine can cause significant swallowing difficulties and airway compromise, potentially requiring surgical intervention.[3]
2. Neurological Disorders: Spinal cord compression (myelopathy) and nerve impingement can lead to a range of neurological deficits, from slowly progressive myelopathy to rapid neurological deterioration after minor injury.[3]
3. Pyogenic Vertebral Osteomyelitis (PVO): Recent research highlights that PVO occurring at DISH-related segments is associated with a significantly higher mortality rate and shorter life expectancy compared to non-DISH-related PVO.[24] The mortality rate in patients with DISH-related PVO was 62% versus 23% in non-DISH-related PVO, with DISH-related PVO identified as an independent risk factor for mortality (adjusted hazard ratio, 2.79).[24] The majority of deaths in this group occurred within one year of diagnosis, often due to sepsis. [24] This increased mortality is hypothesized to be due to DISH-induced spinal instability, which inhibits healing, and the high burden of comorbidities often present in DISH patients. [24]
4. Difficult Intubation and Gastroscopy: The altered anatomy due to ossification, particularly in the cervical spine, can complicate medical procedures requiring access to the upper airways and digestive system.[10]
5. Aspiration Pneumonia: A serious risk for patients with severe dysphagia.[24]

The presence of DISH, especially when complicated by fractures or infections like PVO, significantly worsens the overall prognosis and increases the risk of mortality, underscoring the need for careful management and awareness of these severe complications.[24]

8. Research Gaps and Future Directions

DISH remains incompletely understood. The precise cause of DISH is largely unknown[3], and although metabolic, hormonal, and genetic factors have been implicated, the mechanisms by which these contribute to abnormal bone formation are not fully elucidated[1]. In particular, the specific link between metabolic disorders and ectopic osteogenesis

requires further clarification.[9] Studies examining human leukocyte antigen (HLA) associations have yielded conflicting results,[9] underscoring the need for more definitive genetic research to clarify the role of inherited factors in DISH pathogenesis. Controlled investigations into clinical manifestations and disease progression are scarce. It remains unclear whether pain and swelling are consistently present in involved joints,[12] and whether spinal DISH is inherently a painful condition. Moreover, the etiology of musculoskeletal pain—whether inflammatory or resulting from chronic hyperproliferative changes—has not been resolved.[12] Early bony changes and the continuum of disease progression, from initial ossification to advanced stages, are poorly characterized.[19] This gap hinders early diagnosis and the development of targeted therapeutic strategies that might mitigate progression before extensive ankylosis occurs.

DISH exhibits a strong association with cardiovascular conditions and metabolic syndrome, yet it has not been definitively established whether DISH constitutes an independent cardiovascular risk factor.[33] Disentangling the contribution of DISH itself from shared risk profiles remains essential to understand its impact on cardiovascular morbidity and mortality. Assessment of bone mineral density (BMD) in DISH presents unique challenges. Enthesal ossification and calcifications can falsely elevate BMD readings obtained by dual-energy X-ray absorptiometry (DEXA), thereby obscuring the true degree of intravertebral osteoporosis.[16] Since DISH patients demonstrate an increased risk of vertebral fractures, accurate evaluation of bone density is critical for appropriate management and fracture prevention strategies.

A deeper understanding of early bony changes in DISH could enable earlier diagnosis and foster the development of targeted therapeutic interventions.[33] Recent investigations have identified localized nodules of ectopic mineralization in early-phase DISH,[28] which may serve as sentinel biomarkers for disease onset and offer insight into the initial pathogenic cascade. Identification of such early markers is a priority for translational research aimed at preventing disease progression. Elucidating the pathogenesis of DISH necessitates further exploration of the interplay among genetic, metabolic, hormonal, and vascular factors.[9] In obesity, adipokines may promote osteoblast activity and contribute to ectopic ossification; however, the precise mechanisms by which insulin and other growth factors drive peri-entheseal bone formation remain unclear.[9] Investigating specific genetic loci—such as those involved in Runt-related transcription factor 2 (RUNX2), bone morphogenetic protein (BMP), and Wnt signaling pathways—could reveal novel targets for therapeutic intervention.[16] Functional studies examining how these loci influence osteogenic differentiation and mineralization are particularly warranted.

The intricate interplay between DISH and the gut microbiota represents a compelling frontier. Emerging evidence suggests that microbial composition may modulate DISH-derived pain and influence systemic inflammatory milieu.[20] Delineating the role of specific microbial taxa and their metabolites may uncover new avenues for therapeutic modulation. Fecal microbiome transplantation, in this context, is an exciting area for future investigation;[20] pilot studies exploring microbial community shifts and corresponding clinical outcomes could pave the way for microbiota-based treatments. Therapeutic development for DISH is hindered by a paucity of well-designed efficacy studies.[7] Although observational reports indicate that tumor necrosis factor (TNF) inhibitors may ameliorate pain and reduce osteoproliferative activity in DISH,[7] randomized, double-blind, placebo-controlled trials are required to confirm efficacy and elucidate mechanisms of action—particularly regarding pain modulation and potential anti-inflammatory effects.[30] Robust clinical trials should incorporate quantitative imaging endpoints and validated patient-reported outcome measures to evaluate both structural and symptomatic benefits.

"Clinical trials in a dish" (CTiDs) represent an innovative approach to drug discovery, toxicity testing, and personalized medicine.[34] These in vitro assays offer a more efficient and cost-effective strategy for drug screening, potentially circumventing the translational gap between preclinical research and human trials. [34] By enabling patient-specific drug testing, CTiDs may enhance predictive accuracy and depth before in vivo prescription, and facilitate cross-screening among diverse patient populations.[34] This methodology could accelerate the development of safer, more effective pharmacotherapies for DISH, especially given the challenges associated with conducting traditional clinical trials for rare or complex musculoskeletal conditions. Longitudinal studies are essential to delineate the natural history of DISH, track the progression of ossification, and evaluate the long-term impact of various interventions.[36,37] Such prospective cohorts could better characterize spatiotemporal changes in radiographic and advanced imaging features across all phases of DISH, from early enthesopathic nodules to extensive spinal bridging. Moreover, comprehensive follow-up would yield reliable data on clinical manifestations, functional status, and quality of life—information critical for tailoring management guidelines and prognostic models.[12]

9. Conclusions

DISH epitomizes a complex intersection of systemic metabolic derangement and aberrant osteogenic activity. Although substantial strides have elucidated its epidemiological, genetic, and pathophysiological foundations, critical questions remain—especially regarding the initial entheseal mineralization events and progression to full ankylosis. Recognizing DISH as a sentinel of metabolic syndrome demands comprehensive patient evaluation and interdisciplinary collaboration. Future studies should prioritize prospective cohorts to map disease evolution, integrate molecular and imaging biomarkers, and explore

innovative therapeutic avenues, including targeted anti-inflammatory and metabolic interventions. Bridging descriptive epidemiology with mechanistic research will be essential to transform our conceptual framework. Ultimately, advancing DISH care relies on a cohesive strategy that unites molecular insights, robust clinical trials, and patient-centered outcomes assessment. Energizing collaborative efforts will be crucial to translate insights into tangible patient benefits.

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None.

11. Conflict of Interest

None.

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