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Imaging Features Characterizing the Continuum of Diffuse Idiopathic Skeletal Hyperostosis

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Abstract

Problem: Diffuse idiopathic skeletal hyperostosis (DISH) is a common musculoskeletal condition yet its etiology, early and progressive disease features, and clinical implications are poorly understood. The purpose of this dissertation was to investigate the imaging features associated with the continuum of DISH.

Methods: A retrospective study design was used to evaluate thoracic computed tomography scans from a population in Minnesota, United States. Female and male individuals ≥20 years of age were examined for imaging features of DISH and early-phase DISH. The extent of ectopic bridging between each vertebrae was scored. Subsequently, the individuals with repeated computed tomography scans of the thoracic spine were evaluated for changes in imaging features over time. Lastly, a cohort of cadaveric human thoracic vertebral column specimens were studied to characterize pathological mineralization of the costovertebral joint (CVJ) and its association with DISH.

Findings: DISH was detected in 14.2% of the sample (7.4% of females, 20.9% of males, average age of 78 years) and early-phase DISH was detected in 13.2% of the sample (10.4% of females, 15.8% of males, average age 73 years). The change to early-phase DISH was characterized by new ectopic bridging at previously unaffected regions. Progression in the severity of DISH was characterized by increased bridge scores in regions that were previously affected. Microcomputed tomography demonstrated that ectopic bridging of the CVJ was associated with DISH and intra-articular CVJ mineralization was associated with early-phase DISH.

Significance: Insight into clinical implications of DISH were uncovered through our population-based research. We reported that DISH or early-phase DISH are present in one out of three individuals over the age of 40, with increased prevalence of DISH among males of advanced age. Importantly, we reported on the spatiotemporal changes across the continuum of DISH that differ based on the stage of development. We also identified a potential link between DISH and CVJ mineralization, which may contribute to a modified diagnostic criteria to improve clinical detection. These findings may facilitate improved detection and reporting of DISH in the clinic and, in turn, enhance clinical outcomes for people living with DISH.

Keywords: cadaver; calcification; computed tomography; costovertebral; diffuse idiopathic skeletal hyperostosis; early phase; enthesopathy; epidemiology; human; intervertebral disc; mineralization; ossification; prevalence; retrospective; spine; thoracic; vertebral column; zygapophyseal

Summary for Lay Audience

Arthritis-related musculoskeletal disorders are leading causes of pain and disability worldwide. Back pain and disorders of the spine are especially burdensome. Diffuse idiopathic skeletal hyperostosis (DISH)—a common spine condition—is characterized by irreversible formation of bone-like bridges that connect the bones of the spine. It is estimated based on research from 25 years ago that 15 to 25% of North Americans over 50 years of age are affected by this condition. Importantly, health professionals are often unfamiliar with DISH, so it is often mis- or under-diagnosed. Symptoms generally include back pain and stiffness, and in severe cases, DISH can lead to pinched nerves or obstruct swallowing. The cause of the condition is unknown and there are no effective treatments. Surgery can be performed to remove the mineral bridges, but the recurrence of DISH is extremely high. This poor knowledge and unmet clinical need underscore the necessity of further research.

Our research was designed to address four overarching research questions:

1. What is the current prevalence of DISH and early-phase DISH in a North American population?
2. How often do radiologists report on the imaging features of DISH?
3. How do the bone-like bridges associated with DISH change over time as detected by medical images?
4. What are additional joint structures that could be used to better define DISH?

Using medical records and clinical images, we aimed to determine the impact of DISH along its disease stages across the lifespan. Our studies showed that DISH occurs in one

in four people over the age of 60 years and that more than one third of people over 40 years-of-age displayed either early-phase DISH or DISH. We studied individuals with multiple medical images to learn about changes in DISH over time. Our results identified unique clinical features at different points along the continuum of the disease. Lastly, our new findings show that bony changes at the rib joints are also associated with DISH.

Together, these findings contribute to an important investigation of the clinical features associated with DISH along its continuum with the goal of improving clinical awareness and early detection.

Co-Authorship Statement

Dale E. Fournier is the primary author of all chapters presented in this dissertation.

Comprehensive co-authorship statements are included at the beginning of each chapter.

Table of Contents

List of Abbreviations

CI..Confidence interval

CVJ ....Costovertebral joint

DISH .... Diffuse idiopathic skeletal hyperostosis

IBM ....International Business Machines Corporation

Micro-CT ....Microcomputed tomography

N..Sample (number)

OMC .... Olmsted Medical Center

OR ....Odds ratio

SD .... Standard deviation

SPSS...Statistical Package for the Social Sciences

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Statement of Equity, Diversity, Inclusion, and Decolonization

Given that the research in this dissertation involves humans, we integrated sex-based analyses into the study designs, where possible. The retrospective approach and use of cadaveric specimens from human body donation meant that information related to sex was not directly acquired by our research team. Instead, sex was previously recorded based on biological attributes that are associated with physical and physiological features (e.g., chromosomal genotype, hormonal levels, gross anatomy). The binary sex categorization (i.e., female or male) was likely based on a designation that was assigned at birth based on the visible external anatomy of the newborn. We wish to clarify that for the purposes of this dissertation a binary categorization of sex was used.

We ensured adequate representation in our studies through stratified random sampling and confirm that participants were never excluded based on the dimension of sex. Data analysis and results were intentionally disaggregated by sex and reported regardless of positive or negative outcomes. We referenced the Sex and Gender Equity in Research (SAGER) guidelines checklist during our work.

Chapter 1

General introduction and outline of chapters

This chapter presents an introduction to the anatomy of the human vertebral column, general spinal pathologies, conditions associated with ectopic mineralization (i.e., calcification and/or ossification), and an overview of DISH. Inherent preference was given to studies focused on the thoracic vertebral column and humans. Anatomical position is referenced when describing locations in the human body. In the vertebral column, the terminology of caudal was used to describe direction towards the sacrum and cranial to describe direction towards the skull.

1.1 Anatomy of the human vertebral column

The fundamental unit of the vertebral column is a motion segment, which describes a single intervertebral disc, the adjacent superior and inferior vertebral bodies, and includes all associated tissues connecting the two independent vertebrae. In an adult, the vertebral column is composed of 24 presacral vertebrae that are interspersed by 23 intervertebral discs. The vertebral column is divided into three anatomical regions: i) cervical—seven vertebrae and six intervertebral discs; ii) thoracic—twelve vertebrae and intervertebral discs, and iii) lumbar—five vertebrae and intervertebral discs.

1.1.1 Osseous features of the thoracic vertebral column

Throughout the vertebral column, the morphology of bony features differs slightly based on the region (**Figure 1.1**). From posterior to anterior: spinous process connects to paired transverse processes through the laminas and the transverse process are linked to the vertebral body through the pedicles. In the thoracic region, the mass of the vertebral body is larger than in the cervical region and smaller than in the lumbar region. The projection angle of the spinous processes is prominently in the caudal direction in the thoracic spine.

1.1.2 Articulations of the thoracic vertebral column

There are three articulations in the thoracic vertebral column: i) zygapophyseal joints; ii) CVJs; and iii) intervertebral discs. The first two are synovial joints that are lined with hyaline cartilage, contain synovium, and are surrounded by a fibrous capsule. The latter is a secondary cartilaginous joint that contains fibrocartilage.

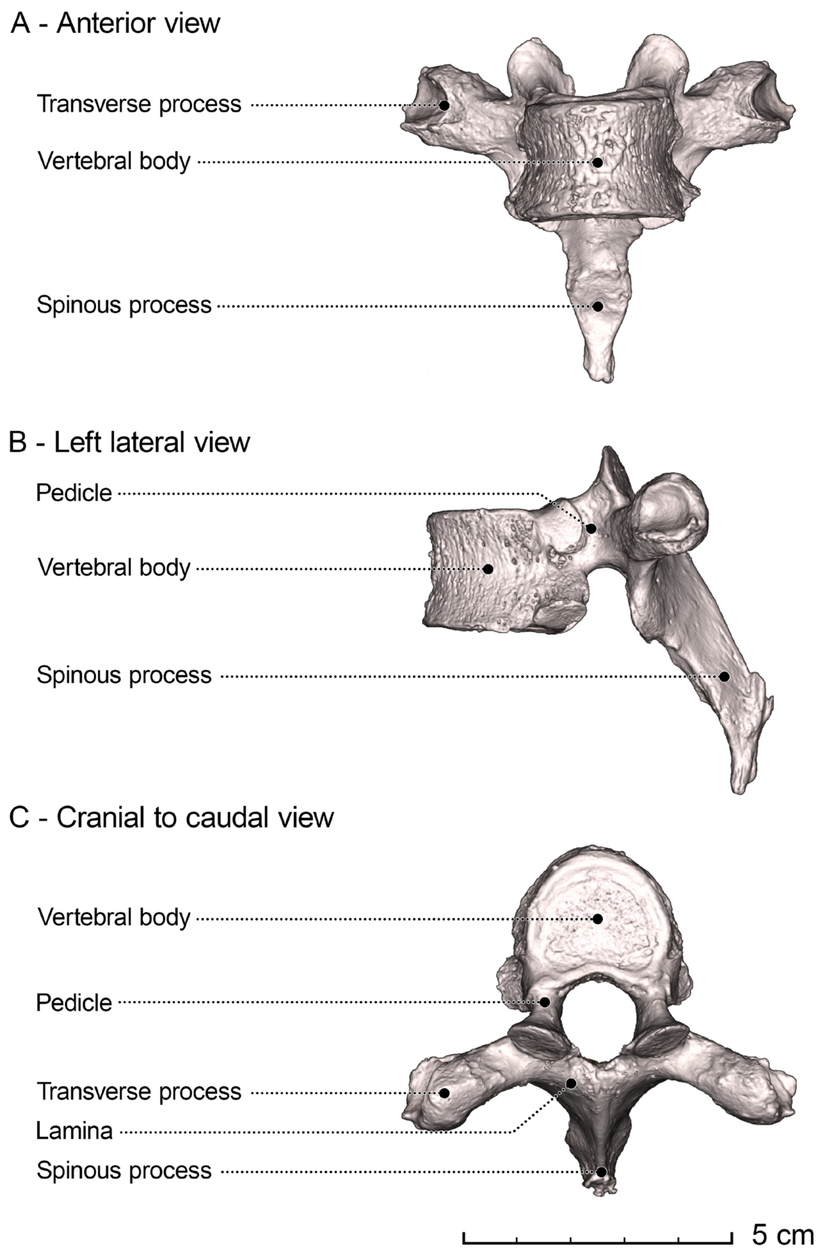

Figure 1.1. Vertebral osseous features

Renderings of an individual thoracic vertebrae with bony landmarks labelled. **A**, Left lateral view; **B**, anterior view; **C**, superior view.

Created by Dale E. Fournier using 3D Slicer (v. 5.2.2), http://www.slicer.org

1.1.2.1 Zygapophyseal joint

Also referred to as apophyseal or facet joints, these structures allow for the interaction of bony prominences within the posterior column of the vertebral column (**Figure 1.2**). Paired superior articulating facets face posteriorly, and paired inferior articulating facets face anteriorly. When viewed in the transverse plane, the angle of the facets ranges from 74 to 88 degrees relative to the midline (1, 2). The thoracic facets are rotated slightly lateral by 16 degrees (1). This restricts flexion and extension of motion segments and facilitates trunk side bending and rotation.

1.1.2.2 Costovertebral joint

The CVJ forms the articulation between the head of the rib and costal surfaces on the vertebrae (**Figure 1.3**). Ribs one, ten, eleven, and twelve articulate alone by a simple synovial joint (3). Ribs two through nine articulate at two sites on the lateral aspect of the vertebrae (inferior costal facet of cranial vertebrae and superior costal facet of caudal vertebrae) and are bisected by an intra-articular ligament creating a double synovial compartment (3). Ribs one through ten attach to the sternum via costal cartilage. True ribs (one through seven) directly attach to the sternum. The motion associated with true ribs is described as a “pump-handle” mechanism. Elevation of the ribs produces rotation of the CVJ through a frontal axis (4, 5). False ribs (eight through ten) merge with the costal cartilage of rib seven to connect to the sternum through the costal cartilage associated with rib seven. The motion associated with true ribs is described as a “bucket-handle” mechanism. Elevation of the ribs produces rotation of the CVJ through a sagittal axis (4, 5). Floating ribs (eleven and twelve) do not attach to the sternum.

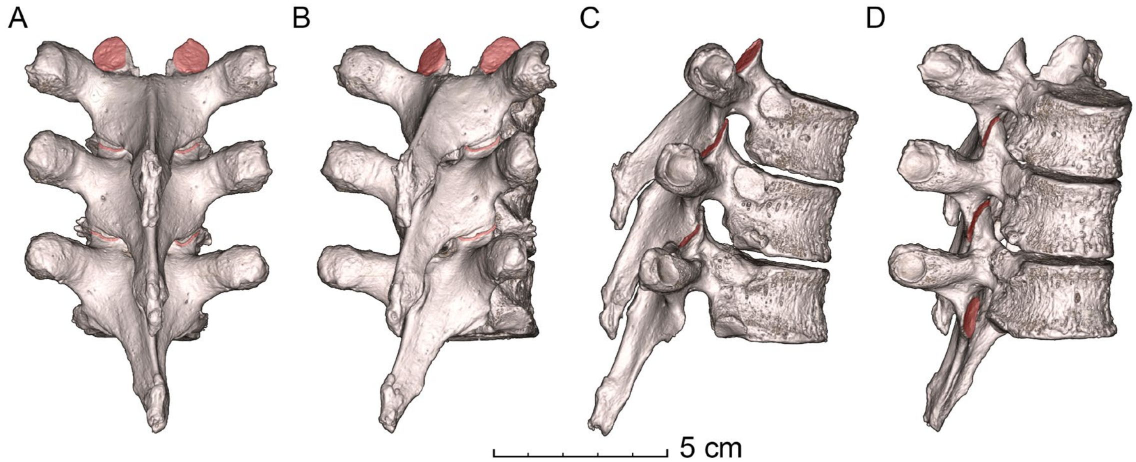

Figure 1.2. Zygapophyseal joint anatomy

Renderings of sequential vertebrae in the thoracic region of the vertebral column, zygapophyseal joints highlighted in red pseudocolouring. **A**, Posterior view; **B**, right posterior-lateral view; **C**, right lateral view; and **D**, right anterior-lateral view.

Created by Dale E. Fournier using 3D Slicer (v. 5.2.2), http://www.slicer.org

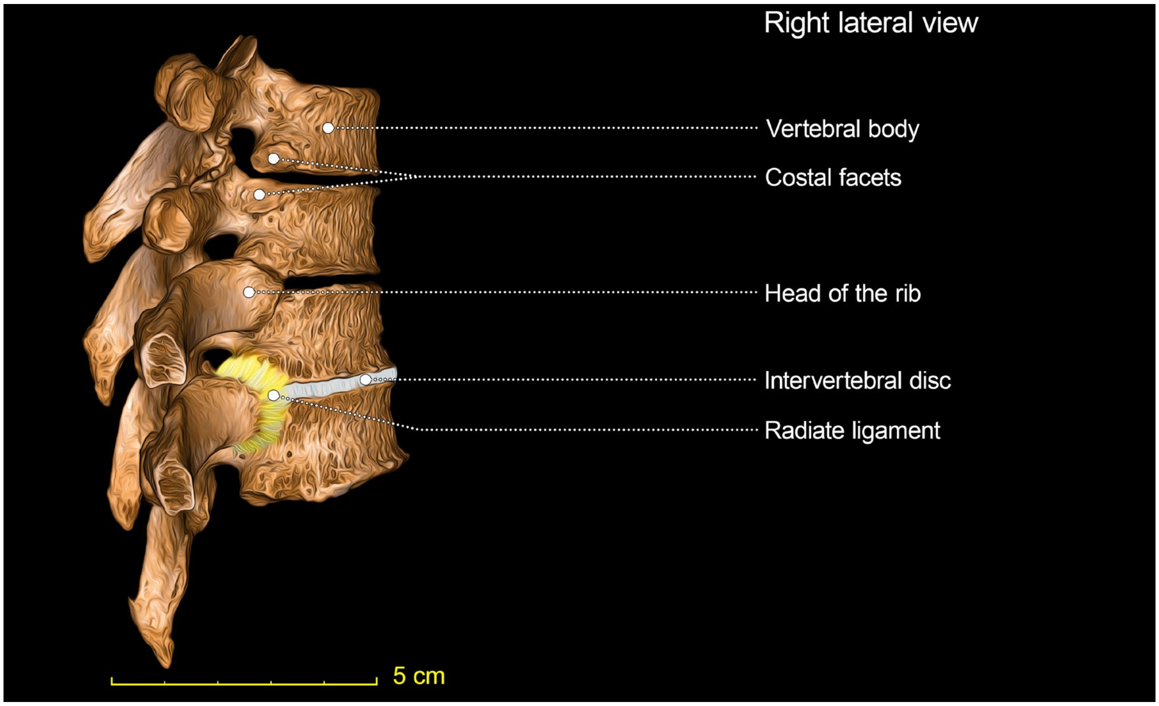

Figure 1.3. Costovertebral joint anatomy

Illustration of sequential thoracic motion segments and the attachment of the head of the rib. Right lateral view with the rib removed at T3-4, ligaments removed at T4-5, and soft tissue illustrated at T5-6.

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Ribs also articulate with the transverse process of the caudal vertebrae associated with a given motion segment; ribs eleven and twelve lack this articulation. The costotransverse ligament fills the space between the neck of the rib and the transverse process (3).

1.1.2.3 Intervertebral disc

Intervertebral discs are complex fibrocartilaginous joint structures that are located between vertebrae. Intervertebral discs stabilize the vertebral column, enable flexibility, and absorb load during weight bearing activities. The intervertebral discs are composed of three distinct yet interdependent tissues: i) anulus fibrosus; ii) nucleus pulposus; and iii) vertebral endplates.

The anulus fibrosus defines the periphery of the intervertebral disc and is characterized by bundles of type one collagen organized into consecutive lamellae (6). This arrangement serves to resist tensile strain experienced during bending, twisting, as well as during compressive loading of the intervertebral disc (7). In a healthy intervertebral disc, the inner anulus fibrosus serves as a transition from the outer fibrous anulus fibrosus to the gelatinous nucleus pulposus, through a decreased abundance of type one collagen and an increase in type two collagen and proteoglycan content, the latter localized to the interlamellar matrix (8).

The nucleus pulposus is the gelatinous central component of the intervertebral disc that is composed of proteoglycans and water within an irregular network of type two collagen and elastin fibers (9). The nucleus pulposus dissipates compressive loads placed on the intervertebral disc. It is an avascular tissue containing a heterogeneous population of chondrocyte-like cells derived from the embryonic notochord (9).

The vertebral endplate is composed of a bilayer of hyaline cartilage and bone that anchor the intervertebral disc to the cranial and caudal vertebrae. The cartilage endplate serves an essential function in nutrient exchange for the intervertebral disc, allowing passive diffusion of nutrients from the adjacent vascularized bone (10).

1.1.3 Connective tissues of the thoracic vertebral column

Numerous intricate connective tissue structures connect between individual motion segment of the vertebral column (**Figure 1.4**). The posterior aspect of the vertebral column is rich with both large and small muscle groups that facilitate gross movements of the trunk. Ligamentous structures function to limit extremes in range of motion. Two broad spanning ligaments are present along the anterior and posterior aspect of the vertebral body: i) anterior longitudinal ligament and ii) posterior longitudinal ligament.

The anterior longitudinal ligament is the only structure present on the anterior aspect of the vertebral column and anchors to the middle of each vertebral body. Within the thoracic spine, the anterior longitudinal ligament is thicker than in the cervical region and narrower compared to the lumbar region (3). This ligament serves to limit excessive hyperextension of the thoracic vertebral column.

The posterior longitudinal ligament is similarly anchored to the middle of each vertebral body, located along the posterior aspect of the vertebral column within the vertebral canal. In the cervical and superior thoracic regions, the posterior longitudinal ligaments are broad and uniform in width; while, in the inferior thoracic and lumbar regions they become narrow over the vertebral bodies and wide over the intervertebral disc (3). These ligaments serve to limit excessive hyperflexion of the thoracic vertebral column.

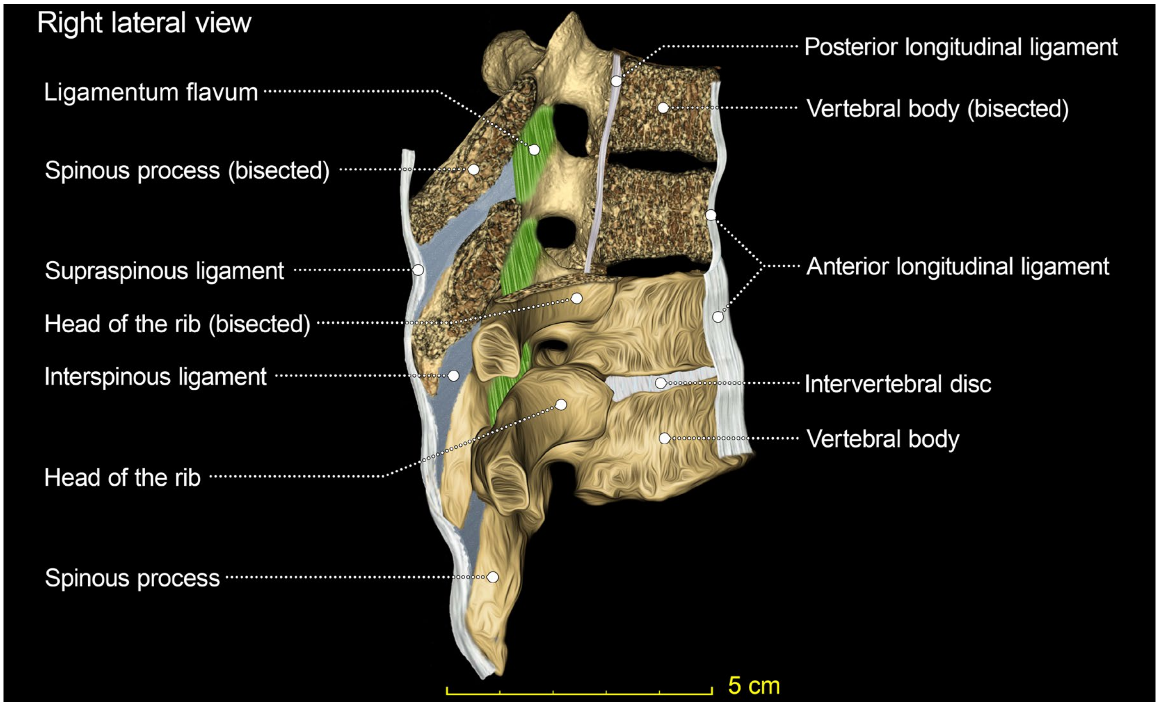

Figure 1.4. Ligaments of the vertebral column

Illustration of sequential thoracic motion segments with ligaments labelled. Lateral view from the right. The top half of the illustration is bisected in the sagittal plane to show additional anatomical features.

Created by Dale E. Fournier using 3D Slicer (v. 5.2.2), http://www.slicer.org

Additional ligamentous structures serve to stabilize the posterior aspect of the vertebral column and maintain normal curvature: i) ligamentum flava; ii) interspinous and intertransverse ligaments; and iii) supraspinous ligaments (**Figure 1.4**).

1.1.3.1 Features of the enthesis

Entheses are specialized tissues that characterize the connection of tendons, ligaments, or joint capsules to bones via fibrocartilaginous tissue (11). The term "enthesitis" describes inflammation of these metabolically active regions (12). Most relevant to the current dissertation is that ectopic mineralization of the enthesis has been described as pathophysiological response to mechanical overloading (12). Pathological bone formation associated with enthesis inflammation can occur throughout the vertebral column and peripheral skeleton.

1.2 Pathologies associated with pathological mineralization

There are numerous pathologies of the vertebral column that are complex and diverse with respect to tissues involved, pathogenesis, and clinical features. In this section, we specifically explore the features of pathological mineralization associated with common spine disorders.

Ectopic mineralization characterizes the deposition of mineral material in regions outside of the skeleton (13). Dystrophic calcification occurs in damaged tissues where there is a notable biochemical abnormality of calcium and phosphate metabolism, or without identifiable cause (i.e., idiopathic) (13). Heterotopic ossification is the formation of bone tissue (woven or organized) with or without cartilage formation (13).

1.2.1 Osteoarthritis

Within the vertebral column, the zygapophyseal joints can involve osteoarthritic changes of joint space narrowing, subarticular bone erosions, subchondral cysts, osteophyte formation, and hypertrophy of the articular process (14). Osteoarthritis in the vertebral column is intimately linked with intervertebral disc degeneration that alters the biomechanics and loading onto the zygapophyseal joints (14). As the intervertebral disc space narrows, osteophytes can form across the anterior or posterior aspect of the vertebral bodies or across zygapophyseal joints. The implication of these space occupying osteophytes can be compression of neural tissues and neurological deficits (14). Degeneration-driven changes also occur at the CVJ, resulting in similar arthritic changes (15, 16)

1.2.2 Spondyloarthropathies

Spondyloarthropathy (or spondyloarthritis) define a family of inflammatory rheumatic diseases that can involve the vertebral column, including: psoriatic and reactive arthritis, ankylosing spondylitis, and undifferentiated spondyloarthritis (i.e., non-radiographic and/or early stage ankylosing spondylitis) (17). Together, these diseases share clinical features, show familial clustering, and are associated with human leukocyte antigen -B27 positivity (17, 18). A characteristic clinical feature of spondyloarthropathy is inflammatory back pain associated with morning stiffness lasting greater than 30 minutes that improves with mobility (17).

1.2.2.1 Ankylosing spondylitis

Ankylosing spondylitis is characterized by sclerosis and/or fusion of the sacro-iliac or zygapophyseal joints (17). In the intervertebral disc, sclerotic regions of the vertebrae ultimately lead to a reactive pathological healing response and ossification of the periphery of the anulus fibrosus. Involvement of the costovertebral and costotransverse joints have been described in ankylosing spondylitis by erosion and sclerosis, bony proliferation, or fusion of the joints (19-21).

1.2.3 Mineralization of spinal ligaments

Previous studies using whole body computed tomography have reported the prevalence of multiple spinal ligament ossification (22-25). One study reported that 58.3% of a Japanese community displayed asymptomatic ossification of spinal ligaments, and that the prevalence increased up to 84% of individuals with body mass index greater than or equal to 30 kg/m^2 (24). Another study from China showed an increased trend in the prevalence of spinal ligament ossification beyond 50 years of age (23). Lastly, analysis of 1,500 consecutive scans for cancer screening in Japan demonstrated regular co-occurrence of spinal ligament ossification within the same individual (22). The prevalence of concomitant spinal ligament ossification differed based on the anatomical region of the vertebral column and the specific ligaments affected (22).

1.2.3.1 Ossification of the posterior longitudinal ligament

Ossification of the posterior longitudinal ligament is characterized by ectopic hyperostosis and calcification of the posterior longitudinal ligament leading to ectopic mineral formation within the vertebral canal (26). The cervical spine is most commonly affected, followed by the thoracic spine. Genetic and familial inheritance have been associated with ossification of the posterior longitudinal ligament, primarily within Asian populations (27). A severe secondary outcome associated with ossification of the posterior longitudinal ligament is direct compression of neural tissues (26, 28). Ossification of the posterior longitudinal ligament often co-exists with ossification of other spinal ligaments (22-25).

1.2.3.2 Ossification of the ligamentum flavum

Ossification of the ligamentum flavum has clinical features similar to ossification of the posterior longitudinal ligament, primarily related to compression of neural tissues. An investigation on the prevalence, morphology, and distribution of ossification of the ligamentum flavum using magnetic resonance imaging reported that 3.8% of 1,736 Chinese volunteers showed imaging features of ossification, predominately in the lower thoracic vertebral column (29). In contrast, another study from China reported that 63.6% of individuals that presented with chest symptoms showed imaging features of ossification of the ligamentum flavum (30). Additional patient studies in Japan and South Korea reported ossification of the ligamentum flavum in 36% and 22% of individuals, respectively (31, 32).

1.2.3.3 Ossification of the supraspinous/interspinous ligaments

The ligaments connecting the spinous processes have not been extensively studied. Few case reports have detailed clinical implications associated with ossification of the supraspinous/interspinous ligaments, some of which include midline thoracolumbar pain (33), cauda equina syndrome (34), post-implant ossification (35), and complication for interlaminar epidural steroid injection (36). A multicenter cross-sectional study in Japan reported that 29% of individuals with ossification of the posterior longitudinal ligament also displayed supra/interspinous ossification (37). Most often, ossification of the supraspinous and/or interspinous ligaments occurred at multiple levels, predominantly in the thoracic vertebral column (37). Another study focused on synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome reported that in these individuals, 63.4% of motion segments showed supraspinous ossification compared to 3.4% that showed ossification of interspinous ligaments (38).

1.2.3.4 Ossification of the anterior longitudinal ligament

Ossification or calcification of the anterior longitudinal ligament is characterized by the formation of ectopic bridges along the anterior aspect of the vertebral column. These pathological features contribute to conditions such as DISH. Ossification of the anterior longitudinal ligament is most commonly reported in the cervical region of the vertebral column in case reports of dysphagia (i.e., difficulty or inability to swallow) (39). Histological examination these structures reported that ectopic ossifications displace or overlay the anterior longitudinal ligament as opposed to forming within the ligament (40). In contrast, others have reported focal regions of dystrophic calcification within the anterior longitudinal ligament of cadaveric tissues (41). In a study from India, the prevalence of ossification of the anterior longitudinal ligament in the cervical region was 5.4% while the prevalence of ossification of the anterior longitudinal ligament in the thoracic region was 32% (25). In Japan, the prevalence of ossification of only the anterior longitudinal ligament was reported to be 13.7% (24). In China, ossification of the anterior longitudinal ligament was identified in the cervical, thoracic, and lumbar regions in 6.6%, 19.2%, and 2% of individuals, respectively (23). Notably, ossification of the anterior longitudinal ligament is often reported to co-exist with ossification of other spinal ligaments (22-25).

1.3 Overview of diffuse idiopathic skeletal hyperostosis

DISH is a non-inflammatory enthesopathy characterized by the formation of ectopic mineral bridges along the anterolateral aspect of the vertebral column. **Figure 1.5** presents a representative image of DISH generated using microcomputed tomography. In 1950, Dr. Jacques Forestier and Dr. Jaume Rotés-Quérol laid down clinical, radiological, and pathological criteria which differentiated a new ankylosing condition of the spine, named "senile ankylosing hyperostosis of the spine" (42). The condition was renamed "ankylosing hyperostosis" to acknowledge its presence in populations other than older adults and the involvement of regions outside of the vertebral column. The name DISH was introduced by Dr. Donald Resnick, Dr. Stephen Shaul, and Dr. Jon Robins to describe this disease (43). Another term of "Forestier's disease" is still commonly used to describe involvement of the cervical vertebral column. Interestingly, regardless of changes in its nomenclature, the bioarcheology record indicates that the condition currently referred to as DISH has been present throughout history based on examination of osseous remains (44).

The underlying etiology of DISH is unknown (45). Epidemiology studies show increased prevalence with advanced age (46-49). The mineral formations associated with DISH appear similar to those seen in ossification of the posterior longitudinal ligament (50). Although DISH often co-exists with other spinal and systemic pathologies, it is

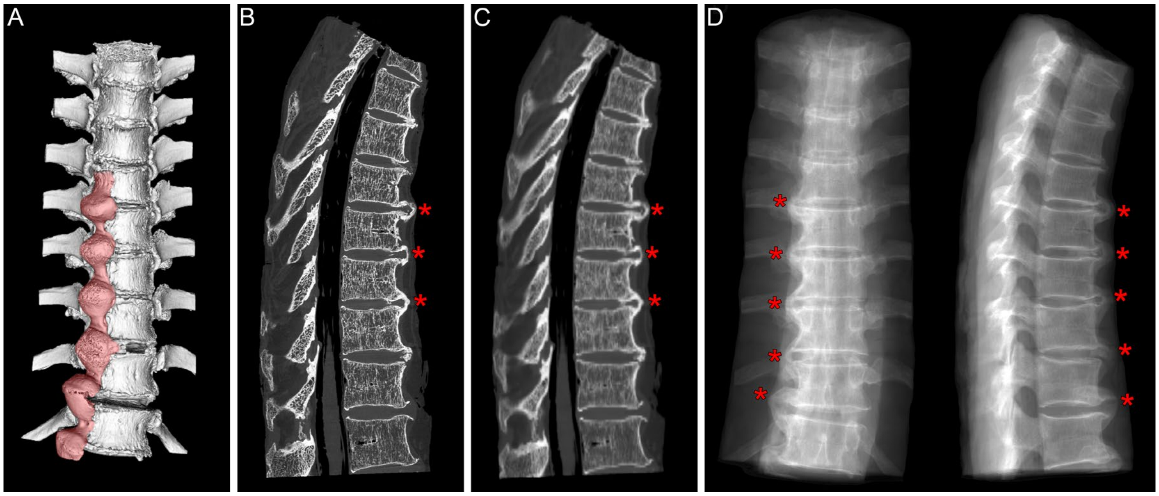

Figure 1.5. Representative images highlighting the key imaging features of DISH

Images were created from microcomputed tomography scan data of the thoracic vertebral column (cut T4 to 12) from a representative 86-year-old female diagnosed with DISH. The characteristic imaging feature of ectopic mineral formation along the anterolateral aspect of the vertebral bodies is highlighted by red pseudocolouring in panel A and by red asterisks in the other panels. **A**, Three-dimensional isosurface rending of mineralized material, anterior view. **B**, Multiplanar reconstructed sagittal slice of microcomputed tomography data (0.154 mm), lateral view. **C**, Rebinned microcomputed tomography scan data to simulate clinical computed tomography (0.616 mm), lateral view. **D**, Digitally reconstructed radiographs to simulate plain-film radiograph, anterior and right lateral views.

advocated as a distinct clinical entity with different prevalence, joint distribution and gender distribution, and pathogenic mechanisms (51).

1.3.1 Medical imaging features

DISH is currently characterized by the detection of biomedical imaging features. It is detected in all regions of the vertebral column with a predominance in the thoracic region. One characteristic feature is the right-sided localization of ectopic bridging that is opposite to the descending aorta. Assessment of vertebral columns with DISH using computed tomography and unique reports of situs inversus totalis (i.e., flipped internal organ location) affirms this clinical feature (52-54). It is hypothesized that the repeated pulsation of the aorta serves to prevent development of ectopic mineral formations directly underneath the aorta (55).

1.3.1.1 Diagnostic criteria from Resnick and Niwayama

The current diagnostic criteria were published in 1976 in the journal Radiology (56). Vertebral involvement was described in a sample of 100 individuals (4 female and 96 male), aged 49 to 88 years (56). The criteria for DISH include:

i. 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
ii. 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

iii. Absence of apophyseal joint bony ankylosis and sacro-iliac joint erosion, sclerosis or bony fusion

Dr. Resnick and Dr. Niwayama noted that deposited bone varied in thickness from 1 up to 20 millimeters and was “bumpy” in front of the intervertebral disc (56). The authors also reported that spine abnormalities were most often continuous; although, five individuals displayed two regions of flowing mineralization separated by an area without bridging (56). The regions spanning thoracic vertebrae seven to ten was the most common region involved (56). Flowing mineralization along all motion segments in the thoracic vertebral column was observed in 32 individuals (56).

1.3.1.2 Criterion for early-phase DISH from Kuperus and colleagues

The diagnosis of DISH is primarily determined based on imaging features of the axial skeleton (57), and a special interest group identified that a mandatory next step to advance the field is classifying early phases of this chronic condition (58). Criteria for detection of early-phase DISH were first proposed in 2019 in a paper published in the journal Radiology (59). First, the authors characterized imaging features of DISH in a cohort of 1,367 male patients over 50 years-of-age that had two chest computed tomography scans at least 2.5 years apart (59). In 90 individuals, DISH was observed in both scans (59). In 55 individuals, DISH was observed in the last scan and not the first scan (grouped as “pre-DISH”) (59). In addition to the pre-DISH group, a random sample of 55 individuals without DISH on either image were assessed for the presence and completeness of a bone bridges at each motion segment (59). Various combinations of bridge scores were assessed and criteria with the best sensitivity of .96 (95% CI=.87, 1.0) and specificity of .94 (95% CI=.85, .99) were selected to distinguish no DISH and early-DISH (59). Early-phase DISH is defined, as follows:

i. A motion segment with a complete bridge (score 3) with an adjacent segment of at least a near-complete bone bridge (score 2 or 3); AND
ii. Another adjacent segment with at least the presence of newly formed bone (score 1 or 2; if the first adjacent segment was score 2, the second adjacent segment may be score 3); OR
iii. When at least three adjacent segments were recorded as showing a near-complete bone bridge (score 2).

Figure 1.6 presents the scoring system and flowchart of the criteria. A second cohort of 2,267 randomly selected people involved in a study of chronic obstructive pulmonary disease with two computed tomography scans available (mean time interval of 5.4 years) were used to validate the criterion (59). The authors reported a sensitivity of .96 (95% CI=.90, 1.0) and a specificity of .83 (95% CI=.82, .85) in the analysis of the second cohort (59).

1.3.2 Clinical profile

In comparison to other musculoskeletal conditions, interest in DISH from a research perspective is scarce and the clinical relevance remains in question (60). Clinical features are expected to progress slowly over a considerable timeframe (45, 61). In 1978, Dr. Donald Resnick proposed three reasons why past reports have failed to delineate the broad clinical spectrum of DISH that remain valid today (62). He specified that DISH is: i) often regarded as a radiographic entity whose clinical manifestations are minor and of

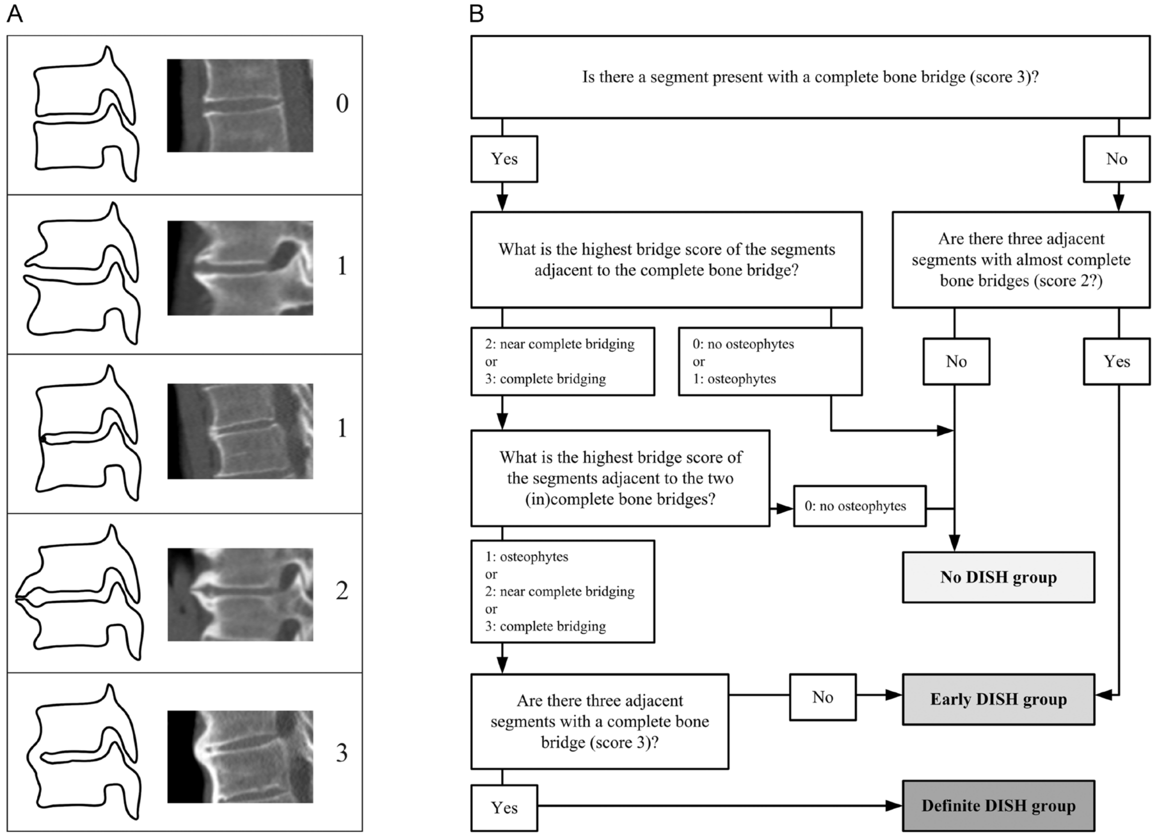

Figure 1.6. Scoring system and flowchart for the application of the early-phase criteria

A, Completeness of ectopic bridging between vertebral bodies is scored using a four-level system. Score of 0: No evidence of ectopic formation. Score of 1: Formations without a solid bridge, separated by more than two millimeters. Score of 2: Near-complete bridging, less than two-millimeter space between structures. Score of 3: Complete bridging in more than two sagittal sections. **B**, Flowchart of the criteria for the diagnosis of early-phase diffuse idiopathic skeletal hyperostosis.

Figure reproduced with permission of the copyright holder: Radiological Society of North America® (**Appendix A**).

Article citation: Kuperus JS, Oudkerk SF, Foppen W, et al. Criteria for Early-Phase Diffuse Idiopathic Skeletal Hyperostosis: Development and Validation. *Radiology*. 2019;291(2):420-426. doi:10.1148/radiol.2019181695 little significance; ii) often co-existing with other rheumatic conditions that obscure related clinical manifestations; and iii) prevalent in older adults with frequent "nonsignificant" complaints that may be paid less attention to by clinicians (62). Further, a potential lack of clinical awareness was described in a study of the clinical and laboratory manifestation of DISH where the referring physician had raised the diagnosis of DISH as a possibility in 4 of 52 individuals that were identified with DISH by the authors (63). A notable clinical feature that is linked to DISH is the occurrence of extra-spinal involvement, commonly at the insertion of the Achilles tendon to the calcaneus, patellar ligament to the tibia, rotator cuff to the humerus, and ligaments of the elbow joint (43, 64-66).

1.3.2.1 Signs and symptoms

In the seminal description, DISH was reported as a "painless" condition mostly characterized by stiffness of the vertebral column (42). In 1985, Dr. Peter Utsinger reported on a case series of 200 people with DISH, which 84% had symptomatic disease characterized by stiffness (most marked in the morning and late evening, precipitated by inactivity, cold, and wet weather) and 72% of individuals also reported pain predominantly localized to the thoracic vertebral column that rarely radiated (64). A controlled study with 56 people with DISH, 43 people with spondylosis, and 31 healthy people indicated that pain and stiffness were greater in people with DISH (63). Evaluation for the 18 tender points (typically applied in populations with fibromyalgia) revealed that people with DISH had a lower pain threshold than people without DISH (67). In contrast, two studies have reported that pain was not associated with DISH and proposed that increased stability of the vertebral column may protect against the development of degenerative changes and, in turn, lead to less back pain (68, 69).

Most studies agree that stiffness of the thoracic vertebral column is a hallmark clinical feature associated with DISH (42, 62-64). Mata and colleagues reported greater Health Assessment Questionnaire (self-rated functional status measure) and Roland-Morris scores (self-rated physical disability caused by low back pain) in people with DISH (63). In addition, the authors reported that all measurements assessing thoracic and lumbar spinal movement were diminished in people with DISH compared to healthy controls (63). Similarly, a study of community-dwelling people in California showed reduced grip strength in people with DISH and greater self-reported difficulty in bending forward (70). Two studies in Japan have recently focused on physical function and DISH. The first evaluated grip strength, one-leg standing time, sit-and-reach, functional reach, and Oswestry Disability Index (self-rated score of level of function in activities of daily living in those rehabilitating from low back pain) and the EuroQuol-5D (self-rated level of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) in 504 volunteers, in which DISH was detected in 4.3% of female and 14.3% of male individuals (71). The authors reported no inter-group differences in physical function (71). In the second study, physical function was evaluated within a group of 255 individuals at baseline and after an interval of six years, in which 15.3% of individuals displayed imaging features of DISH at baseline (72). The authors reported little effect of DISH progression on longitudinal physical function (72).

1.3.2.2 Relevant associations

While the underlying etiology and pathogenesis of DISH are uncertain (45), various associations have been established based on clinical and epidemiological studies. Studies of prevalence of DISH have showed increased detection in male individuals of advanced age (46, 47). Instances of DISH have also been associated with obesity, high waist-to-hip circumference ratio, dyslipidemia, hypertension, glucose intolerance, type II diabetes, hyperuricemia, hyperinsulinemia, and possibly elevated growth hormone and insulin-like growth factor 1 levels (45, 73).

1.3.3 Therapies and treatments

The primary therapeutic goals associated with DISH are to reduce pain and stiffness, address metabolic dysfunction, prevent adverse complications, and ultimately prevent or delay the progression of ectopic mineralization (74). Surgical resection of ectopic mineral is performed when symptoms are severe (e.g., dysphagia). One problem is that the re-occurrence of ectopic mineralization is high in individuals with DISH, with or without symptoms (75-77). Another problem is the poor prognosis for recovery following surgery. A study of individuals with DISH and cervical hyperextension injuries that underwent spinal surgery reported that 66% of individuals experienced preoperative complications and 52.3% survival rate five years after the procedure, with the most common cause of death related to pneumonia (78). The authors concluded that reduced thoracic mobility is a cause of poor prognosis in people with cervical injuries and DISH (78).

Conservative treatments are often indicated yet their success is not well characterized. Only one study involving exercise therapy for 15 individuals living with DISH has been published in 2008 (79). The authors described considerable symptoms of pain and stiffness at baseline and implemented 24 weeks of an exercise-based program focused on strengthening, mobility, and stretching (79). The exercise program was most effective at alleviating stiffness and improving ability to bend forward at the trunk (79).

1.4 Overview of dissertation

1.4.1 Rationale for current studies

As a clinical entity, DISH is a prevalent musculoskeletal condition that is poorly understood with respect to its etiology, progression, clinical implications, and clinical management. The current radiographic criteria and definition of DISH limits detection to an advanced disease state although newly validated criteria enable the categorization of early disease features. The purpose of the studies presented in this dissertation are to characterize imaging features across the continuum of DISH.

1.4.2 Aim I

In North America, the single prevalence study of DISH used 2,364 plain-film radiographs from individuals over the age of 50 years in Minnesota and reported that 15 percent of female and 25 percent of male individuals had DISH based on Resnick's radiographic criteria (46). Given that the study was conducted over 25 years ago yet remains the most recent report on the prevalence of DISH in North America, we sought to provide an update on the prevalence of DISH. At the same time, we designed the first study to explore the prevalence of early-phase DISH in a population-based sample. The first aim of this dissertation was to evaluate the prevalence of DISH and early-phase DISH across the lifespan and among both sexes in a large population-based sample. It was hypothesized that DISH would be more prevalent than previously reported 25 years prior, and that early-phase DISH would be more common than DISH in a population in America.

1.4.3 Aim II

In the past, others have acknowledged that DISH is underreported and underdiagnosed (60). As part of the first study, the radiology report associated with each thoracic computed tomography scan was evaluated to determine if it included a clinical description of DISH. The second aim of this dissertation focused on characterizing the frequency of accurate reporting of DISH in a cohort of thoracic computed tomography scans. It was hypothesized that DISH as a clinical entity would be underreported in a sample of adults referred for thoracic computed tomography.

1.4.4 Aim III

To date, few studies have detailed the progression of changes in imaging features associated with DISH beyond the formation of additional contiguous bridges of the vertebral column (80, 81). This limitation is primarily attributed to availability of repeated spine imaging given costs to the health care system and risks of exposure to radiation from medical imaging. Moreover, the progression of DISH is thought to occur over a lengthy period (61). Therefore, the third aim of this dissertation was to characterize changes in imaging features across the continuum of DISH is a population of people that received multiple computed tomography scans of the thoracic vertebral column as part of previous medical care. It was hypothesized that better understanding the progression of ectopic mineralization in the spine will elucidate unique clinical features of DISH and better inform on the disease continuum.

1.4.5 Aim IV

To date, the characteristic imaging feature of DISH remains the presence of ectopic mineral formations along the anterolateral aspect of the spine. Previous studies have indicated that DISH—described as an enthesopathy—can involve additional joint structures beyond the spine (66). Others have described impairment in respiratory function associated with DISH (82, 83). The fourth aim of this dissertation was to conduct a detailed characterization of CVJ involvement in DISH using micro-CT scans of the thoracic spine from cadaveric specimens. It was hypothesized that mineralization of the CVJ would be associated with DISH and that characterization of these changes would provide a novel anatomical site of pathological changes that can be evaluated to further classify DISH.

1.4.6 Dissertation hypothesis

In this dissertation it was hypothesized that characterization of imaging features across the continuum of DISH will highlight unique features that can be used to differentiate DISH, identify early disease, and improve understanding of clinical implications.

1.5 References

1. Panjabi MM, Oxland T, Takata K, et al. Articular facets of the human spine:Quantitative three-dimensional anatomy. Spine. 1993;18(10):1298-310.

2. Ebraheim NA, Xu R, Challgren E, et al. Quantitative anatomy of the cervical facet and the posterior projection of its inferior facet. Journal of Spinal Disorders. 1997;10(4):308-16.

3. Standring SE-i-C. Gray's anatomy: The anatomical basis of clinical practice. Forty-Second edition ed. Amsterdam: Elsevier; 2021.

4. Beyer B, Sholukha V, Dugailly PM, et al. In vivo thorax 3d modelling from costovertebral joint complex kinematics. Clinical Biomechanics. 2014;29(4):434-8.

5. Beyer B, Van Sint Jan S, Chèze L, et al. Relationship between costovertebral joint kinematics and lung volume in supine humans. Respiratory Physiology and Neurobiology. 2016;232:57-65.

6. Humzah MD, Soames RW. Human intervertebral disc: Structure and function. The Anatomical Record. 1988;220(4):337-56.

7. Cassidy JJ, Hiltner A, Baer E. Hierarchical structure of the intervertebral disc. Connective Tissue Research. 1989;23(1):75-88.

8. Eyre DR, Muir H. Quantitative analysis of types i and ii collagens in human intervertebral discs at various ages. BBA - Protein Structure. 1977;492(1):29-42.

9. Pattappa G, Li Z, Peroglio M, et al. Diversity of intervertebral disc cells: Phenotype and function. Journal of Anatomy. 2012;221(6):480-96.

10. Urban JPG, Smith S, Fairbank JCT. Nutrition of the intervertebral disc. Spine. 2004;29(23):2700-9.

11. Benjamin M, Kumai T, Milz S, et al. The skeletal attachment of tendons - tendon 'entheses'. Comparative Biochemistry and Physiology - A Molecular and Integrative Physiology; 2002: Elsevier Inc.; 2002. p. 931-45.

12. Schett G, Lories RJ, D'Agostino MA, et al. Enthesitis: From pathophysiology to treatment. Nature Reviews Rheumatology. 2017;13(12):731-41.

13. Smith R, Wordsworth P. Ectopic mineralization. In: Smith R, Wordsworth P, editors. Oxford Textbook of Clinical and Biochemical Disorders of the Skeleton: Oxford University Press; 2016. p. 0.

14. Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: The facet joints. Nature Reviews Rheumatology. 2013;9(4):216-24.

15. Nathan H, Weinberg H, Robin GC, et al. The costovertebral joints. Anatomical-clinical observations in arthritis. Arthritis & Rheumatism. 1964;7(3):228-40.

16. Sanzhang C, Rothschild BM. Zygapophyseal and costovertebral/costotransverse joints: An anatomic assessment of arthritis impact. Rheumatology. 1993;32(12):1066-71.

17. Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. New England Journal of Medicine. 2016;374(26):2563-74.

18. Van Tubergen A, Weber U. Diagnosis and classification in spondyloarthritis: Identifying a chameleon. Nature Reviews Rheumatology. 2012;8(5):253-61.

19. Pascual E, Castellano JA, López E. Costovertebral joint changes in ankylosing spondylitis with thoracic pain. Rheumatology. 1992;31(6):413-5.

20. Shouval A, Croitoru S, Keret S, et al. Costovertebral joint involvement in radiographic axial spondyloarthritis: A case-series computed tomography study. International Journal of Rheumatic Diseases. 2023;26(5):977-81.

21. Bochkova AG, Levshakova AV, Bunchuk NV, et al. Spinal inflammation lesions as detected by magnetic resonance imaging in patients with early ankylosing spondylitis are more often observed in posterior structures of the spine. Rheumatology (Oxford, England). 2010;49(4):749-55.

22. Fujimori T, Watabe T, Iwamoto Y, et al. Prevalence, concomitance, and distribution of ossification of the spinal ligaments results of whole spine ct scans in 1500 japanese patients. Spine. 2016;41(21):1668-76.

23. Liang H, Liu G, Lu S, et al. Epidemiology of ossification of the spinal ligaments and associated factors in the chinese population: A cross-sectional study of 2000 consecutive individuals. BMC Musculoskeletal Disorders. 2019;20(1).

24. Endo T, Takahata M, Koike Y, et al. Association between obesity and ossification of spinal ligaments in 622 asymptomatic subjects: A cross-sectional study. Journal of Bone and Mineral Metabolism. 2022;40(2):337-47.

25. Singh NA, Shetty AP, Jakkepally S, et al. Ossification of posterior longitudinal ligament in cervical spine and its association with ossified lesions in the whole spine: A cross-sectional study of 2500 ct scans. Global Spine Journal. 2023;13(1):122-32.

26. Matsunaga S, Sakou T. Ossification of the posterior longitudinal ligament of the cervical spine: Etiology and natural history. Spine. 2012;37(5):E309-E14.

27. Yoshimura N, Nagata K, Muraki S, et al. Prevalence and progression of radiographic ossification of the posterior longitudinal ligament and associated factors in the japanese population: A 3-year follow-up of the road study. Osteoporosis International. 2014;25(3):1089-98.

28. Baptiste DC, Fehlings MG. Pathophysiology of cervical myelopathy. Spine Journal. 2006;6(6 SUPPL.):S190-S7.

29. Guo JJ, Luk KDK, Karppinen J, et al. Prevalence, distribution, and morphology of ossification of the ligamentum flavum: A population study of one thousand seven hundred thirty-six magnetic resonance imaging scans. Spine. 2010;35(1):51-6.

30. Lang N, Yuan HS, Wang HL, et al. Epidemiological survey of ossification of the ligamentum flavum in thoracic spine: Ct imaging observation of 993 cases. European Spine Journal. 2013;22(4):857-62.

31. Mori K, Kasahara T, Mimura T, et al. Prevalence, distribution, and morphology of thoracic ossification of the yellow ligament in japanese; results of ct-based cross-sectional study. Spine. 2013;38(19):E1216-E22.

32. Kim SI, Ha KY, Lee JW, et al. Prevalence and related clinical factors of thoracic ossification of the ligamentum flavum—a computed tomography-based cross-sectional study. Spine Journal. 2018;18(4):551-7.

33. Simpson S, Krabak BJ. Interspinous ligament calcification in a collegiate gymnast. PM and R. 2014;6(8):742-5.

34. Weiss MH, Spencer GE. Ossification of a lumbar interspinous ligament with compression of the cauda equina. A case report. The Journal of bone and joint surgery American volume. 1970;52(1):165-7.

35. Tian NF, Zhang XL, Wu YS, et al. Fusion after interspinous device placement. Orthopedics. 2012;35(12):e1822-5.

36. Bilim S, Şencan S, Gündüz OH. An unusual obstacle to the thoracic interlaminar epidural injection for the treatment of post-herpetic neuralgia. Agri. 2023;35(1):44-7.

37. Mori K, Yoshii T, Hirai T, et al. Prevalence and distribution of ossification of the supra/interspinous ligaments in symptomatic patients with cervical ossification of the posterior longitudinal ligament of the spine: A ct-based multicenter cross-sectional study. BMC Musculoskeletal Disorders. 2016;17(1):1-7.

38. Xu W, Li C, Zhao X, et al. Whole-spine computed tomography findings in sapho syndrome. Journal of Rheumatology. 2017;44(5):648-54.

39. Harlianto NI, Kuperus JS, Mohamed Hoesein FAA, et al. Diffuse idiopathic skeletal hyperostosis of the cervical spine causing dysphagia and airway obstruction: An updated systematic review. Spine J. 2022;22(9):1490-503.

40. Kuperus JS, Smit EJM, Pouran B, et al. Anterior longitudinal ligament in diffuse idiopathic skeletal hyperostosis: Ossified or displaced? Journal of Orthopaedic Research. 2018;36(9):2491-6.

41. Fournier DE, Kiser PK, Beach RJ, et al. Dystrophic calcification and heterotopic ossification in fibrocartilaginous tissues of the spine in diffuse idiopathic skeletal hyperostosis (DISH). Bone Research. 2020;8(1).

42. Forestier J, Rotes-Querol J. Senile ankylosing hyperostosis of the spine. Annals of the rheumatic diseases. 1950;9(4):321-30.

43. Resnick D, Shaul SR, Robins JM. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier's disease with extraspinal manifestations. Radiology. 1975;115(3):513-24.

44. Littlejohn GO. Historical bioarcheological aspects of diffuse idiopathic skeletal hyperostosis in humans. Seminars in Arthritis and Rheumatism. 2022;52.

45. Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: Clinical features and pathogenic mechanisms. Nature Reviews Rheumatology. 2013;9(12):741-50.

46. Weinfeld RM, Olson PN, Maki DD, et al. The prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in two large american midwest metropolitan hospital populations. Skeletal Radiology. 1997;26(4):222-5.

47. Westerveld LA, Quarles Van Ufford HME, Verlaan JJ, et al. The prevalence of diffuse idiopathic skeletal hyperostosis in an outpatient population in the netherlands. Journal of Rheumatology. 2008;35(8):1635-8.

48. Nardo L, Lane NE, Parimi N, et al. Diffuse idiopathic skeletal hyperostosis association with thoracic spine kyphosis: A cross-sectional study for the health aging and body composition study. Spine. 2014;39(24):E1418-E24.

49. Yoshihara H, Nadarajah V, Horowitz E. Prevalence and characteristics of thoracic diffuse idiopathic skeletal hyperostosis in 3299 black patients. Scientific Reports. 2021;11(1).

50. Resnick D, Guerra Jr J, Robinson CA, et al. Association of diffuse idiopathic skeletal hyperostosis (DISH) and calcification and ossification of the posterior longitudinal ligament. American Journal of Roentgenology. 1978;131(6):1049-53.

51. Mader R. Diffuse idiopathic skeletal hyperostosis: A distinct clinical entity. Israel Medical Association Journal. 2003;5(7):506-8.

52. Verlaan JJ, Westerveld LA, Van Keulen JW, et al. Quantitative analysis of the anterolateral ossification mass in diffuse idiopathic skeletal hyperostosis of the thoracic spine. European Spine Journal. 2011;20(9):1474-9.

53. Kuperus JS, Buckens CF, Šprem J, et al. The natural course of diffuse idiopathic skeletal hyperostosis in the thoracic spine of adult males. Journal of Rheumatology. 2018;45(8):1116-23.

54. Sebro R. Confirmation of the influence of descending aorta on osteophyte formation in dish. Journal of Clinical Rheumatology. 2018;24(6):351-3.

55. Mori K, Yayama T, Nishizawa K, et al. Aortic pulsation prevents the development of ossification of anterior longitudinal ligament toward the aorta in patients with diffuse idiopathic skeletal hyperostosis (DISH) in japanese: Results of chest ct-based cross-sectional study. Journal of Orthopaedic Science. 2019;24(1):30-4.

56. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology. 1976;119(3):559-68.

57. Mader R, Baraliakos X, Eshed I, et al. Imaging of diffuse idiopathic skeletal hyperostosis (DISH). RMD Open. 2020;6(1).

58. Mader R, Verlaan JJ, Eshed I, et al. Diffuse idiopathic skeletal hyperostosis (DISH): Where we are now and where to go next. RMD Open. 2017;3(1).

59. Kuperus JS, Oudkerk SF, Foppen W, et al. Criteria for early-phase diffuse idiopathic skeletal hyperostosis: Development and validation. Radiology. 2019;291(2):420-6.

60. Verdone F. Diffuse idiopathic skeletal hyperostosis in the third millennium: Is there (yet) cause for concern? Journal of Rheumatology. 2010;37(6):1356-7.

61. Yaniv G, Bader S, Lidar M, et al. The natural course of bridging osteophyte formation in diffuse idiopathic skeletal hyperostosis: Retrospective analysis of consecutive ct examinations over 10 years. Rheumatology (United Kingdom). 2014;53(11):1951-7.

62. Resnick D, Shapiro RF, Wiesner KB, et al. Diffuse idiopathic skeletal hyperostosis (DISH) [ankylosing hyperostosis of forestier and rotes-querol]. Seminars in Arthritis and Rheumatism. 1978;7(3):153-87.

63. Mata S, Fortin PR, Fitzcharles M-A, et al. A controlled study of diffuse idiopathic skeletal hyperostosis. Medicine (Baltimore). 1997;76(2):104-17.

64. Utsinger PD. Diffuse idiopathic skeletal hyperostosis. Clinics in Rheumatic Diseases. 1985;11(2):325-51.

65. Belanger TA, Rowe DE. Diffuse idiopathic skeletal hyperostosis: Musculoskeletal manifestations. The Journal of the American Academy of Orthopaedic Surgeons. 2001;9(4):258-67.

66. Mader R, Sarzi-Puttini P, Atzeni F, et al. Extraspinal manifestations of diffuse idiopathic skeletal hyperostosis. Rheumatology. 2009;48(12):1478-81.

67. Mader R, Novofastovski I, Rosner E, et al. Nonarticular tenderness and functional status in patients with diffuse idiopathic skeletal hyperostosis. Journal of Rheumatology. 2010;37(9):1911-6.

68. Schlapbach P, Beyeler CH, Gerber NJ, et al. Diffuse idiopathic skeletal hyperostosis (dish) of the spine: A cause of back pain? A controlled study. Rheumatology. 1989;28(4):299-303.

69. Holton KF, Denard PJ, Yoo JU, et al. Diffuse idiopathic skeletal hyperostosis and its relation to back pain among older men: The mros study. Seminars in Arthritis and Rheumatism. 2011;41(2):131-8.

70. Katzman WB, Huang MH, Kritz-Silverstein D, et al. Diffuse idiopathic skeletal hyperostosis (DISH) and impaired physical function: The rancho bernardo study. Journal of the American Geriatrics Society. 2017;65(7):1476-81.

71. Banno T, Togawa D, Hasegawa T, et al. The controlled study of diffuse idiopathic skeletal hyperostosis for the assessment of physical function in elderly populations. Journal of Orthopaedic Science. 2018;23(6):929-34.

72. Li S, Banno T, Hasegawa T, et al. Long-term effects of diffuse idiopathic skeletal hyperostosis on physical function: A longitudinal analysis. Journal of Orthopaedic Science. 2023.

73. Gantenbein B, May RD, Bermudez-Lekerika P, et al. Egr2, igf1 and il6 expression are elevated in the intervertebral disc of patients suffering from diffuse idiopathic skeletal hyperostosis (dish) compared to degenerative or trauma discs. Applied Sciences (Switzerland). 2021;11(9).

74. Mader R. Current therapeutic options in the management of diffuse idiopathic skeletal hyperostosis. Expert Opinion on Pharmacotherapy. 2005;6(8):1313-8.

75. Miyamoto K, Sugiyama S, Hosoe H, et al. Postsurgical recurrence of osteophytes causing dysphagia in patients with diffuse idiopathic skeletal hyperostosis. European Spine Journal. 2009;18(11):1652-8.

76. Vodičar M, Košak R, Vengust R. Long-term results of surgical treatment for symptomatic anterior cervical osteophytes: A case series with review of the literature. Clinical Spine Surgery. 2016;29(9):E482-E7.

77. von der Hoeh NH, Voelker A, Jarvers JS, et al. Results after the surgical treatment of anterior cervical hyperostosis causing dysphagia. European Spine Journal. 2015;24:489-93.

78. Sawakami K, Watanabe K, Sato T, et al. Rib hyperostosis as a risk factor for poor prognosis in cervical spine injury patients with diffuse idiopathic skeletal hyperostosis. Spine. 2020;45(5):300-8.

79. Al-Herz A, Snip JP, Clark B, et al. Exercise therapy for patients with diffuse idiopathic skeletal hyperostosis. Clinical rheumatology. 2008;27(2):207-10.

80. Murakami Y, Morino T, Hino M, et al. Imaging features of early diffuse idiopathic skeletal hyperostosis (pre-DISH): Analysis of progression of ligament ossification over 5 years by computed tomography. Spine Surgery and Related Research. 2023;Advance Online Publication.

81. Murakami Y, Morino T, Hino M, et al. Progression of ossification of the anterior longitudinal ligament associated with diffuse idiopathic skeletal hyperostosis by age: A study of computed tomography findings over 5 years. Global Spine Journal. 2021;11(5):656-47.

82. Oudkerk SF, Buckens CF, Mali WPTM, et al. Diffuse idiopathic skeletal hyperostosis is associated with lower lung volumes in current and former smokers. American Journal of Respiratory and Critical Care Medicine. 2016;194(2):241-2.

83. Oudkerk SF, Hoesein FAAM, Öner FC, et al. Diffuse idiopathic skeletal hyperostosis in smokers and restrictive spirometry pattern: An analysis of the copdgene cohort. Journal of Rheumatology. 2020;47(4):531-8.

Chapter 2

Prevalence of Diffuse Idiopathic Skeletal Hyperostosis (DISH) and Early-phase DISH Across the Lifespan of an American Population

Authored by Dale E. Fournier, Andrew E. Leung, Michele C. Battié, and Cheryle A. Séguin.

2.1 Co-authorship statement

Chapter 2 is adapted from Fournier DE, Leung AE, Battié MC, and Séguin CA, (2023). Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) and early-phase DISH across the lifespan of an American population. *Rheumatology*. https://doi.org/10.1093/rheumatology/kead362. Figures and text are reproduced with permission of the copyright holder: Oxford University Press (**Appendix B**).

Dale E. Fournier lead study design with contributions from MCB and CAS. Dale E. Fournier performed data collection, analysis, and illustrations. AEL contributed clinical expertise and to inter-rater reliability. Manuscript was written by Dale E. Fournier with suggestions from CAS and critically revised by AEL and MCB.

2.2 Chapter summary

DISH is a common musculoskeletal condition; however, the imaging features and disease continuum from early to advanced is poorly understood. The purpose of this study was to evaluate the prevalence of DISH and early-phase DISH in an American population and to assess the extent and pattern of ectopic mineral formation across the thoracic spine.

Data were retrieved in collaboration with the Rochester Epidemiology Project. We conducted a retrospective image evaluation of a sample of individuals over 19 years-of-age with computed tomography of the thoracic spine from a Northern United States catchment area. Stratified random sampling by age and sex was used to populate the study. We examined the prevalence and extent of ectopic mineral along the thoracic spine using previously established criteria.

A total of 1,536 unique images (766 female and 770 male individuals) including 16,710 motion segments were evaluated for imaging features of the continuum of DISH. Collectively, 40.5% of all motion segments evaluated displayed evidence of ectopic mineral formation in the thoracic spine. The prevalence of early-phase DISH was 13.2% (10.4% of female and 15.8% of male individuals). The prevalence of established DISH was 14.2% (7.4% of female and 20.9% of male individuals). Remarkable heterogeneity was detected in individuals within each disease classification, based on the extent of the thoracic spine affected and degree of mineralization.

The continuum of imaging features associated with DISH is detected in more than one in four adults and both sexes in an American population.

2.3 Introduction

DISH is a non-inflammatory enthesopathy characterized by ectopic mineral bridges that form along the anterolateral aspect of the spine (1). Diagnosis of DISH is based on radiographic criteria reported by Resnick and Niwayama in 1976: ectopic mineral bridges across four contiguous vertebrae; preserved intervertebral disc height; and lack of bony ankylosis of the sacro-iliac joints or zygapophyseal joints in the involved areas (2). Ectopic bridges present as osteophyte-like outgrowths or thin flowing bands of mineralized tissue predominately on the right side of the thoracic spine (3-5). Clinically, DISH has been linked to stiffness and disrupted physical function (6,7). In severe cases, ectopic bridges can cause dysphagia and/or airway obstruction (8). DISH is also associated with an increased risk of incidental vertebral fracture (9-12). Currently, the etiology of DISH is unknown and there are no disease-modifying treatments (13).

Advanced medical imaging has enhanced the sensitivity to detect features of DISH compared to standard radiographs (5,14). Recent studies using Resnick and Niwayama's criteria and computed tomography imaging report prevalence rates ranging from 3.9 to 30.8% (14-26, **Table 2.1**). DISH is reported more frequently in male than female individuals (2:1 ratio, **Table 2.1**). Although DISH is most often diagnosed in older adults (14-26), case reports have described instances of DISH in individuals as young as 24 years of age (27). Since the diagnosis of DISH is limited to advanced disease due to criteria centered on involvement of contiguous vertebrae (2), the pathogenesis and features associated with the onset and progression of DISH are largely unknown (28-30)

Table 2.1. Summary of prevalence studies of DISH from published literature

Ref	Region	Population studied	Age range (years)	Study sample (Male:Female ratio)	Prevalence of DISH (Male%, Female%)
14	JPN	Hospital—Nonsurgical	40 to 89	558 (1.16)	27.2% (38.7, 14.0)
15	JPN	Screening—Cancer	21 to 94	1500 (1.45)	12.0% (16.0, 6.2)
16	JPN	Screening—Pulmonary disease	16 to 97	3013 (1.39)	8.7% (13.1, 2.5)
17	JPN	Trauma	20 to 90+	1479 (2.24)	19.5% (21.1, 16.0)
18	KOR	Hospital—Nonsurgical	30 to 100	164 (1.04)	24.4% (31.7, 15.8)
19	SWE	Hospital—Emergency	40 to 89	418 (1.73)	24.4% (32.5, 10.5)
20	CHN	Screening—Cancer	22 to 95	2000 (2.01)	3.9% (4.9, 1.8)
21	PAK	Hospital—Nontraumatic	50 to 65	416 (1.85)	30.8% (38.8, 23.3)
22	ICL	Population study—CVD	68 to 96	5321 (0.75)	7.5% (13.7, 2.8)
23*	USA*	Trauma*	5 to 103	3299 (1.19)	7.7% (7.0, 8.6)
24	IND	Trauma	20 to 98	1815 (4.01)	19.1% (14.9, 20.2)
25	JPN	Hospital—Emergency	79 ± 10	1519 (1.21)	17.4% (12.2, 5.3)
26	IND	Trauma	31 to 81+	2500 (2.17)	6.9% (8.2, 4.1)

Notes: Based on computed tomography and Resnick and Niwayama's diagnostic criteria. Three letter abbreviation indicates the country where the research was conducted. *Preferentially selected population of African-American and Caribbean-American individuals. CVD, cardiovascular disease; DISH, diffuse idiopathic skeletal hyperostosis.

Recently, criteria for early-phase DISH have been developed and validated (29) but have yet to be applied in studies of disease prevalence.

In the current study, we investigated the continuum of DISH by examining the prevalence and pattern of ectopic spine mineralization for early-phase DISH and DISH across the adult lifespan in an American population. We hypothesized that DISH would be more common than previously reported and that early-phase DISH would be prominent based on computed tomography of the thoracic spine throughout the adult lifespan.

2.4 Methods

2.4.1 Data source and study design

A retrospective evaluation of a cross-sectional dataset of computed tomography scans of the thoracic spine was conducted with the Rochester Epidemiology Project. This platform enables population-based research through an established medical records system that links health information across providers in Minnesota (31). Medical information is recorded as part of routine medical practice and not standardized across professions. Electronic indexes that can be searched included demographic data, diagnostic and procedural codes, and drug prescriptions. In 2002, the Health Insurance Portability and Accountability Act introduced a new level of regulation that enabled passive medical record review to be conducted without obtaining study-specific written informed consent from each participant if the investigators obtain a waiver from the Mayo Clinic and Olmsted Medical Center Institutional Review Board. This study was approved by the Institutional Review Boards of Mayo Clinic (20-000640, **Appendix C**) and Olmsted Medical Center (008-OMC-20, **Appendix D**).

We studied computed tomography images from individuals who received spinal imaging between 1995 and 2019 at Mayo Clinic (Rochester, Minnesota), identified using 2019 Radiology Current Procedural Terminology codes for the thoracic spine (72128-30). The reported pixel resolution ranged from 0.6 to 1.1 mm. Individuals 20 years of age and older were included to assess the prevalence of DISH across the adult lifespan using an individual's most recent thoracic spine computed tomography (5,444: 46.7% female and 53.3% male individuals). An age- and sex-stratified random sampling approach was used to populate each decade of life with 100 female and 100 male individuals. A priori reasons for exclusion were established so that confounding anatomical changes (e.g., severe deformity and/or ankylosing spondylitis) and limitations in computed tomography images (e.g., without sagittal/frontal views, restricted field of view) were excluded.

2.4.2 Image evaluation for radiographic features of DISH

The list of 1,600 computed tomography images were randomized to reduce order bias. Multi-planar reconstructed images were viewed in QREADS Clinical Image Viewer (Version 5.14.0, Mayo Clinic) with a set window and level (2500 and 350, respectively). Demographic information was known at the time of evaluation.

DISH was diagnosed using Resnick and Niwayama's criteria (2, 31) (**Figure 2.1A**). A validated scoring system (29) was used to assess the extent of ectopic bridging at each thoracic motion segment (**Figure 2.1B**). The sacro-iliac joints were not assessed since thoracic computed tomography scans were retrieved, instead the zygapophyseal joints were evaluated for structural changes of inflammation. Early-phase DISH was

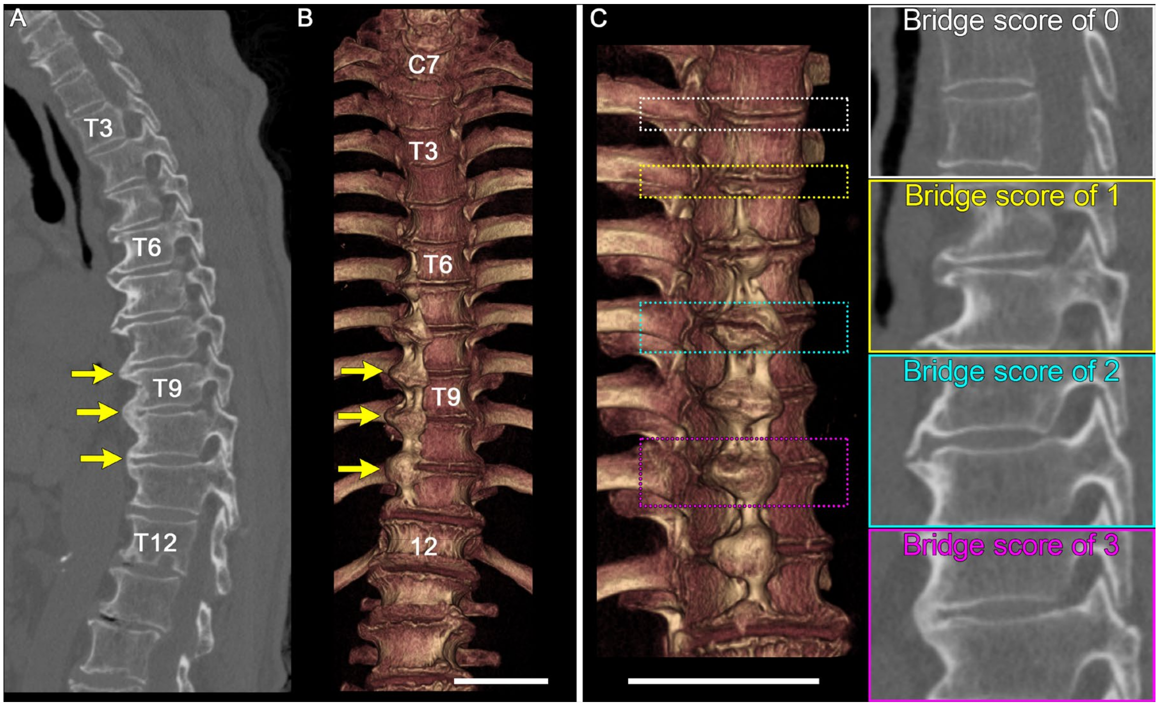

Figure 2.1. Representative computed tomography images and renderings of DISH

A, Sagittal computed tomography of the thoracic spine from a representative 75 year old male meeting the diagnostic criteria for DISH; region of three contiguous complete bridges highlighted by yellow arrows. **B**, Three-dimensional rendering of the thoracic spine from the same individual. **C**, Magnified three-dimensional rendering of the same spine rotated to showcase the right anterolateral aspect of the thoracic spine from T4 to T11. Outlined regions provide representative examples of the scoring system applied at the level of the motion segment: Score of 0 indicates no bridging; score of 1 indicates anterior formations greater than one mm apart; score of 2 indicates an almost complete bridge (less than one mm apart); and score of 3 indicates a complete bridge. Scale bar represents 5 cm.

determined using validated criteria (29). Briefly, when a complete bridge was identified the adjacent motion segments were evaluated for either a near-complete or complete bridge (score of 2 or 3). If present, then the next adjacent motion segment was evaluated for any form of ectopic bridging (score of 1, 2, or 3), which determined early-phase DISH. Three contiguous motion segments with near-complete bridging (score of 2) was also designated as early-phase DISH (29). Images from individuals that did not meet either criteria for DISH or early-phase DISH were assigned to the "without" group.

Prior to data collection and following training, an inter-rater evaluation was performed using a random sample of 20 thoracic computed tomography scans from a local hospital. Unknown at the time of evaluation was that 11 individuals did not show evidence of either early-phase DISH or DISH (55%), 5 individuals met the criteria for early-phase DISH (25%), and 4 individuals met the criteria for DISH (20%). The linearly weighted kappa statistic for inter-rater identification of DISH or early-phase DISH was perfect (κ=1.0).

We focused on ensuring reliable inter-rater evaluation of bridge score prior to data collection. Within the same sample of 20 individuals (and associated 204 motion segments), at least 12% of motion segments displayed complete bridges (score of 3), 15% of motion segments displayed near-complete bridges (score of 2), and 32% of motion segments displayed some anterior bridging (score of 1). Therefore, at least 60% of motion segments displayed pathological features of ectopic bridging, for which the raters reported substantial agreement in scoring (κ=.89; 95% CI= .84, .94). After which, DEF independently evaluated all scans.

Following data collection, an intra-rater reliability analysis for consistency in diagnosis and scoring of ectopic bridging was performed. A random sample of 20 thoracic computed tomography scans were identified from the randomized dataset. Five scans were identified from each quartile (based on order assessed) of the data to evaluate potential change in the reliability of reporting over time. Unknown at the time of evaluation was that 12 individuals did not show evidence of either early-phase DISH or DISH (60%), 3 individuals met the criteria for early-phase DISH (15%), and 5 individuals met the criteria for DISH (25%). The linearly weighted kappa statistic for intra-rater identification of DISH or early-phase DISH was .94 (95% CI=.83, 1.0).

Within the same sample of 20 individuals for intra-rater analysis (and associated 220 motion segments), at least 14% of motion segments displayed complete bridges (score of 3), 14% of motion segments displayed near-complete bridges (score of 2), and 18% of motion segments displayed some anterior bridging (score of 1). Therefore, at least 45% of motion segments displayed pathological features of ectopic bridging, for which substantial intra-rater agreement was achieved in scoring .82 (95% CI=.76, .88).

2.4.3 Statistical methods

Analyses were performed using SPSS Statistics (Version 26.0, IBM Corp., Armonk, New York). Normality was evaluated with Shapiro-Wilks' test, which indicated the need for non-parametric tests with continuous age data. Chi-squared tests were used to evaluate differences in frequencies. Post-hoc testing was performed using adjusted standardized residuals with Bonferroni's multiple comparisons. Mann-Whitney U tests were used to analyze differences between sexes and Kruskal-Wallis tests for pairwise comparisons across disease categories.

2.5 Results

2.5.1 Sample characteristics

Of the 1,600 computed tomography images evaluated, 1,536 were included (**Table 2.2**) and 85.0% of the individuals were "white." The predominant indication for computed tomography of the thoracic spine was trauma-related (79.8%). Other indications were neurological impairments (10.2%), follow-up or screening (4.4%), query for fracture (4.0%), or surgical relevance (1.7%). In total, 16,710 motion segments were analyzed with an average of 1,519 ± 9 for each thoracic vertebral level.

2.5.2 Prevalence of DISH across the adult lifespan

Images from 202 individuals (13.2%: 80 females and 122 males) met the criteria for early-phase DISH (**Figure 2.2A**) and images from 218 individuals (14.2%: 57 females and 161 males) met the criteria for DISH (**Figure 2.2B**), totaling 420 individuals with any phase of DISH (27.3%, **Figure 2.2C**).

A greater proportion of male individuals presented with early-phase DISH compared to female individuals (39.6% female, 60.4% male, p=.01). Similarly, there were significantly more male compared to female individuals with DISH (26.1% female, 73.9% male, p<0.001). The group that did not meet the criteria for any phase of DISH (72.7%) was composed of more female than male individuals (56.4% female, 43.6% male1, p<0.001). No age differences were found between sexes within each group. Among female individuals, the prevalence of early-phase DISH and DISH was 10.4%

Table 2.2. Number and mean age of individuals with computed tomography images of the thoracic spine available from the total sample of 1600 by 10-year age interval and sex

Age group	Total Sample		Female Individuals		Male Individuals	
	N (%)	Mean ± SD	N (%)	Mean ± SD	N (%)	Mean ± SD
20-29	202 (13.2)	24.4 ± 2.7	98 (12.8)	23.9 ± 2.5	104 (13.5)	24.9 ± 2.7
30-39	191 (12.4)	34.4 ± 2.8	98 (12.8)	34.5 ± 2.8	93 (12.1)	34.3 ± 2.9
40-49	194 (12.6)	44.8 ± 3.0	97 (12.7)	44.8 ± 3.0	97 (12.6)	44.7 ± 2.9
50-59	189 (12.3)	54.8 ± 2.8	97 (12.7)	54.9 ± 2.7	92 (11.9)	54.6 ± 3.0
60-69	189 (12.3)	64.4 ± 2.9	95 (12.4)	64.3 ± 3.0	94 (12.2)	64.5 ± 2.8
70-79	193 (12.6)	74.5 ± 2.8	97 (12.7)	74.6 ± 2.9	96 (12.5)	74.4 ± 2.8
80-89	202 (13.2)	84.9 ± 2.9	97 (12.7)	85.0 ± 2.8	105 (13.6)	84.8 ± 3.1
90+	176 (11.5)	93.1 ± 2.9	87 (11.4)	93.4 ± 3.1	89 (11.6)	92.8 ± 2.8
Total	1536	59.0 ± 22.9	766 (49.9)	58.9 ± 22.9	770 (50.1)	59.1 ± 22.9

Notes: N, number; mean corresponds to age; SD, standard deviation. Excluded images (not included in table): 64 individuals (34 females and 30 males), no significant age difference between sexes (median age = 56, 20 to 97 years).

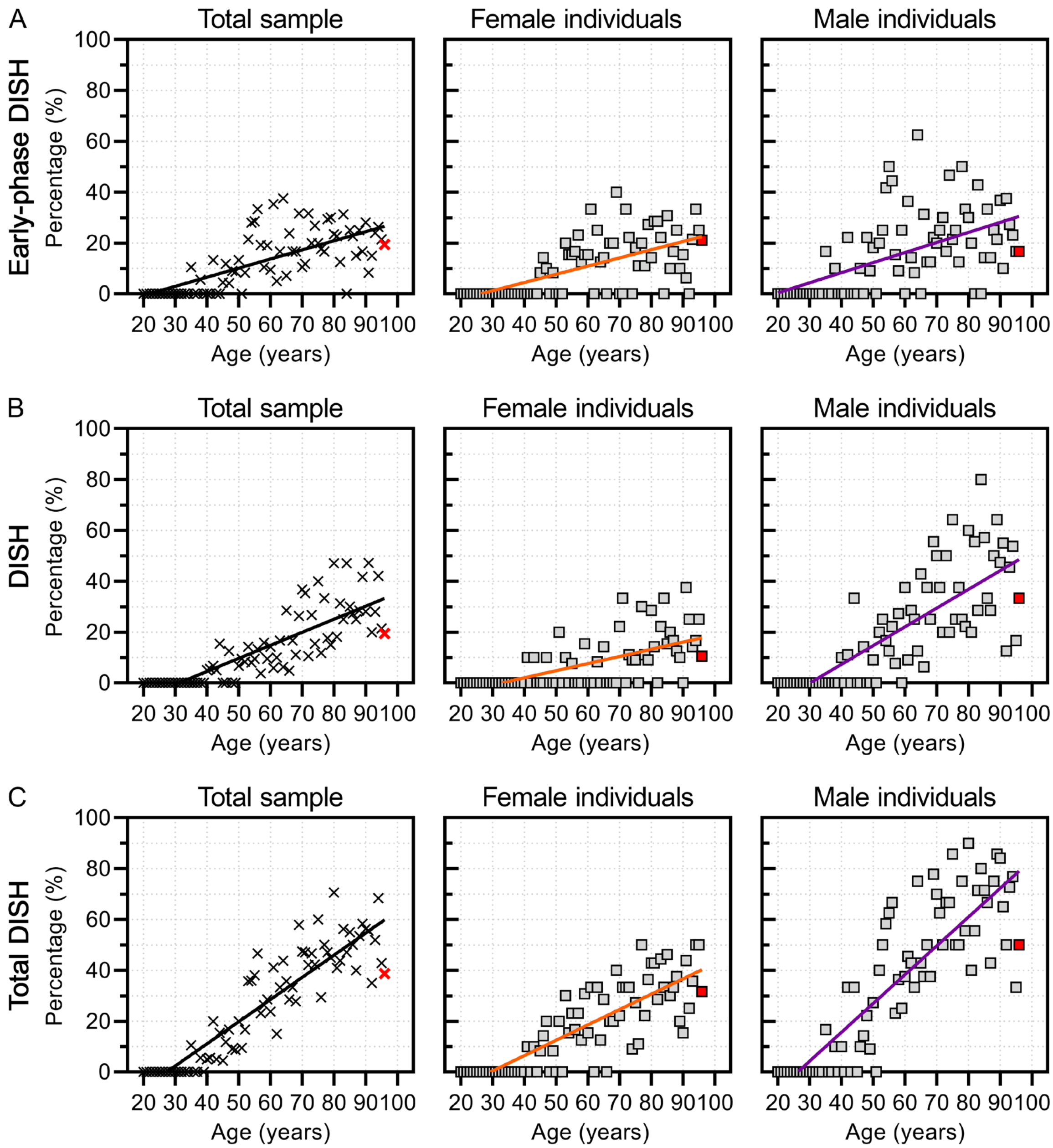

Figure 2.2. Prevalence of the continuum of DISH

A, Early-phase DISH (n = 202), (**B**) DISH (n = 218), and (**C**) either early-phase DISH or DISH (n = 420) from the total sample of 1,536 individuals across the adult lifespan and stratified by sex. Each data point represents the percentage of individuals affected per age. The average sample size for each data point is 19.8 ± 4.5 individuals (female = 9.8 ± 3.0 and male = 10.0 ± 3.2). Red symbols indicate pooling of data of those 96 years and older because of reduced sample size for each distinct age (total group = 30 cases, females = 18 and males = 12).

and 7.4%, respectively. Among male individuals, the prevalence of early-phase DISH and DISH was 15.8% and 20.9%, respectively.

A positive correlation was found between any phase of DISH and advanced age in both sexes (**Figure 2.2C**). The median age of individuals with DISH was significantly higher than those without (81 years, range 40 to 104 compared to 49 years, 20 to 103) ($p<0.001$). The median age of individuals with early-phase DISH (74 years, 35 to 102) was also significantly higher than the without group ($p<0.001$), and statistically lower than those with DISH ($p=.02$).

The youngest individual identified with early-phase DISH was 35 years of age. Over 34 years of age, the prevalence of early-phase DISH was 16.4%: 13.0% of female and 19.7% of male individuals (**Figure 2.2A**). The youngest individual identified with DISH was 40 years of age. Over 39 years of age, the prevalence of DISH was 19.1%: 10.0% of female and 28.1% of male individuals (**Figure 2.2B**). Nearly one in ten individuals (9.7%) displayed imaging features of either early-phase DISH or DISH by 60 years of age (**Figure 2.2C**). After 60 years of age, nearly one in two individuals (45.4%) met the criterion for early-phase DISH or DISH (**Figure 2.2C**).

The prevalence of DISH was assessed among all individuals for each decade of life (**Figure 2.3**). This analysis revealed a significant increase in the prevalence of all phases of DISH in individuals between their 30s and 40s (5.2-fold) and 40s and 50s (1.9-fold). In both sexes, a notable increase in the prevalence of early-phase DISH was noted between individuals in their 40s and 50s.

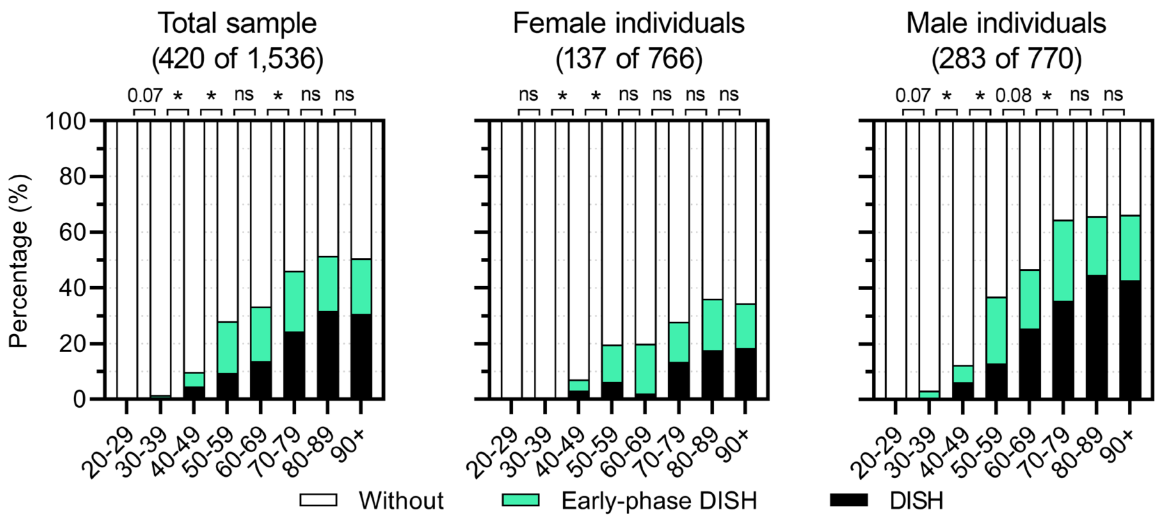

Figure 2.3. Prevalence of early-phase DISH and DISH stratified by decade of life and sex

Data represented as the percentage of individuals with each diagnosis per decade of life. White bars represent those that did not meet the criteria for either early-phase DISH or DISH, green bars represent early-phase DISH, and solid bars represent distinguished DISH. Sequential decades were evaluated with Mann Whitney U test, statistical significance of P<0.05 denoted by asterisk.

2.5.3 Imaging characteristics of early-phase thoracic DISH

Images from individuals meeting the criteria for early-phase DISH were assessed to better characterize features along the disease continuum (**Figure 2.4**). Complete bridging between two contiguous vertebrae was detected in 82.2% of individuals with early-phase DISH and on average involved 1.6 ± 1.2 motion segments (range one to five) per individual (**Figure 2.4A**). Presentations included: a single motion segment with a complete bridge (34.9%); at least one site of two contiguous motion segments bridged (22.3%); two motion segments with complete bridges separated by at least one motion segment without a complete bridge (25.3%); or a combination of the above (17.5%). No significant age or sex differences were detected in the frequency of early-phase DISH presentations. Marked heterogeneity was also noted in the localization and extent (bridge score) of ectopic bridging across the thoracic spine (**Figure 2.5A**).

When evaluating the entire thoracic spine, over half (53.5%) of those with early-phase DISH met the criteria in more than one way depending on the specific motion segments examined and the direction of evaluation (i.e., cranial/caudal) (**Figure 2.4B**). The most common presentations were a complete bridge with two near-complete bridges (3-2-2: 43.6%) and three contiguous near-complete bridges (2-2-2: 38.6%).

While the criteria for early-phase DISH requires three adjacent motion segments affected by ectopic bridging, the average number of motion segments with evidence of any ectopic mineral was 8.2 ± 2.0 and ranged from 3 to 11 (**Figure 2.4C**). Moreover, when the bridging scores for all thoracic motion segments from each individual with early-phase DISH were summed, the average score was 15 (range 6 to 24) (**Figure 2.4C**).

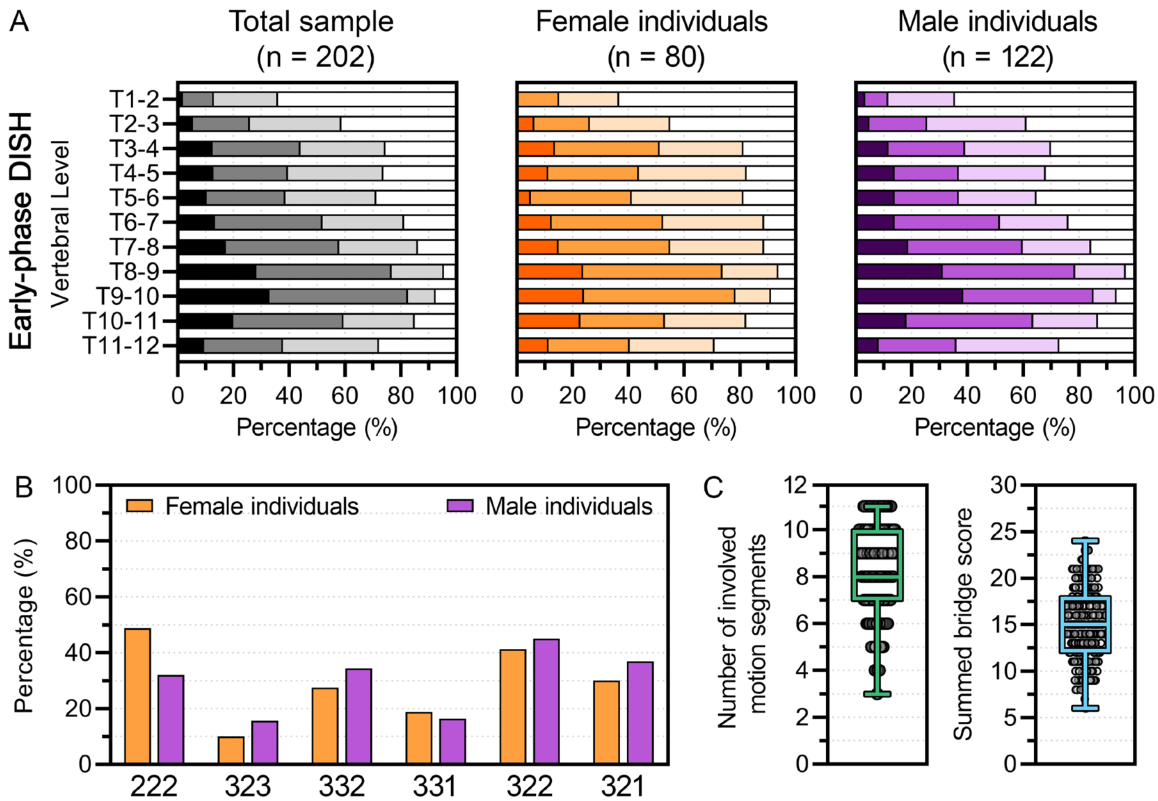

Figure 2.4. Imaging characteristics of early-phase DISH

A, Anatomical distribution of ectopic bridging in individuals meeting the criteria for early-phase diffuse idiopathic skeletal hyperostosis (n = 202 individuals, including: 80 female and 122 male). Darkest bars represent complete bridging (score of 3); medium bars represent near-complete bridging (score of 2); light bars represent anterior formations (score of 1); and white bars represent no bridging (score of 0). **B**, Frequency that each presentation was observed in the sample with early-phase DISH, stratified by sex. Presentations detected in either the superior or inferior direction are combined in this graph. **C**, Analysis of the entire thoracic spine from individuals with early-phase DISH. The total number of motion segments with ectopic bridging (ranging from the required minimum of 3 up to all 11 segments) and the summed thoracic spine bridging scores (ranging from the lowest possible score of 6 up to 24). Data presented as box-and-whisker plots with tails representing the minimum and maximum values. Each data point represents one individual.

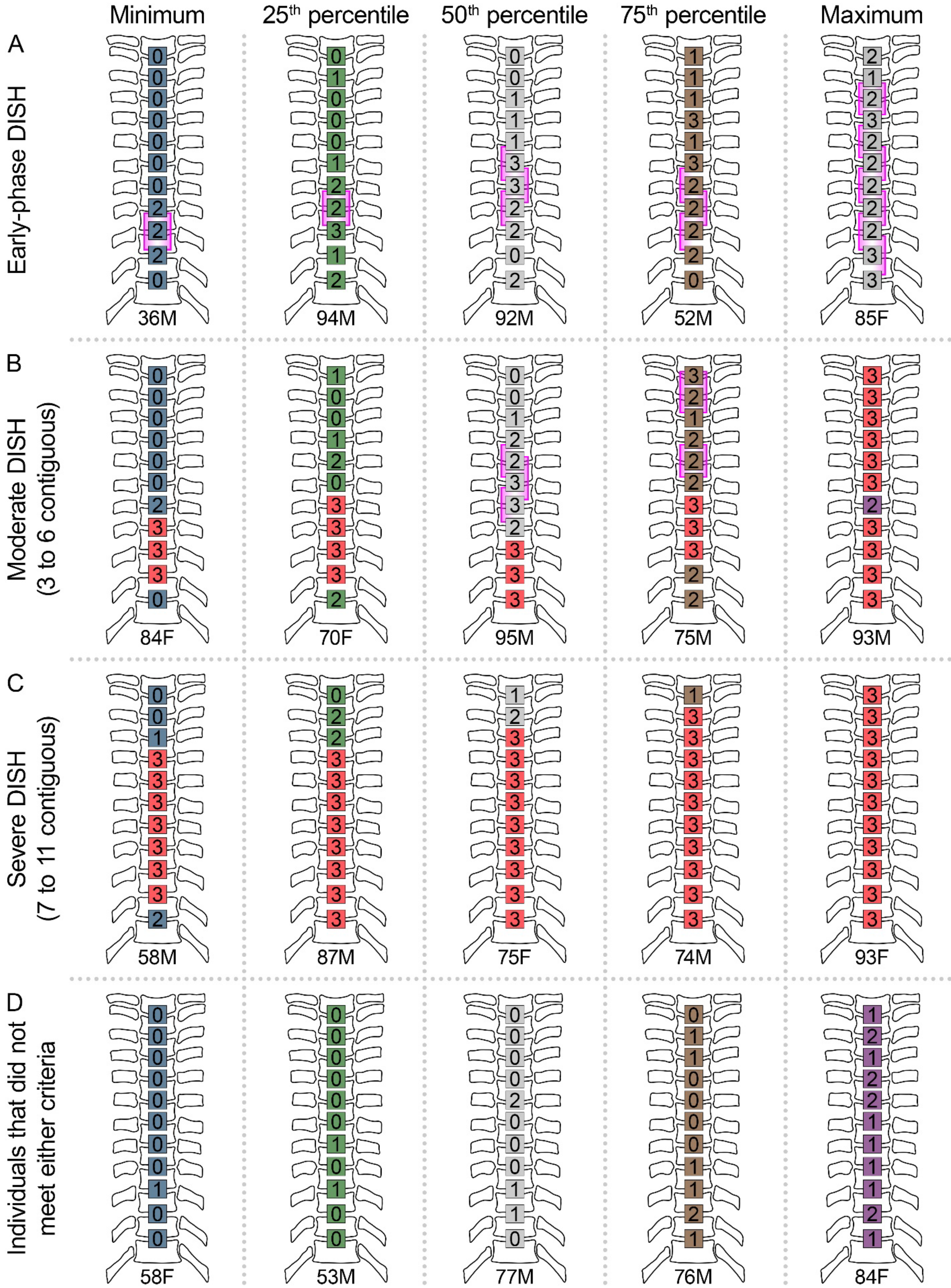
Minimum
25th percentile
50th percentile
75th percentile
Maximum
A
Early-phase DISH
36M
94M
92M
52M
85F
B
Moderate DISH
(3 to 6 contiguous)
84F
70F
95M
75M
93M
C
Severe DISH
(7 to 11 contiguous)
58M
87M
75F
74M
93F
D
Individuals that did not
meet either criteria
58F
53M
77M
76M
84F

Figure 2.5. Visualization of the extent of thoracic spine involvement and heterogeneity of ectopic bridging score within all groups

Individuals within each group were evaluated for the number of motion segments with ectopic bridging and the total summed bridging score across the thoracic spine. These values were used to stratify the group into minimum (blue), 25th percentile (green), 50th percentile (grey), 75th percentile (brown), and maximum (magenta) values. Percentiles were established based on two factors: i) number of motion segments with evidence of ectopic bridging and ii) summed bridge score of the thoracic spine. Unique three contiguous motions segments with ectopic mineralization that fulfilled the criteria for early-phase DISH are represented by the pink boxes. Contiguous regions of completed bridging that fulfilled Resnick and Niwayama's diagnostic criteria are represented by the red colours boxes. Each schematic displays the imaging features of representative individuals within each of these categories, with age and sex of each individual indicated below (F = female, M = male). The scoring system validated by Kuperus and colleagues to score ectopic bridging: 0 = no bridging; 1 = anterior formations greater than 1 mm apart; 2 = near-complete bridge of less than 1 mm; or 3 = complete bridge

These metrics underscore the heterogeneity in the imaging features of individuals with early-phase DISH. Neither age nor sex significantly influenced the number of motion segments with ectopic mineralization in those with early-phase DISH.

2.5.4 Imaging characteristics of thoracic DISH

The anatomical pattern of spine mineralization was likewise assessed in images from individuals with DISH (**Figure 2.6**). Complete bridging of motion segments characteristic of DISH was observed throughout the thoracic spine (**Figure 2.6A**). In fact, 60.1% of all motion segments in images from individuals with DISH displayed complete bridging, with more than 50% involvement at each spine level from T4 to T12. The most common presentation of ectopic mineral was a single contiguous band (94.0%). Twelve individuals showed two distinct regions of ectopic bridging that each met the diagnostic criteria for DISH. The hallmark right-sided predominance of ectopic mineral associated with DISH (4, 5) was also noted.

Three contiguous complete bridges—the threshold for diagnosis—was detected in 22.9% of individuals with DISH. The average number of contiguous motion segments with complete bridging was 5.9 ± 2.6 (range 3 to 11). There were no age- or sex-related differences related to the number of contiguous bridges. Regardless of sex, individuals with DISH could be sub-classified based on the number of contiguous complete bridges in the thoracic spine (**Figure 2.6B**). Over half the individuals with DISH (62.4%) showed between three and six contiguous motion segments with complete bridging (median age = 80, 40 to 100 years), predominantly in the lower thoracic spine. The remaining 37.6% of individuals with DISH showed seven or more contiguous motion segments (median age =

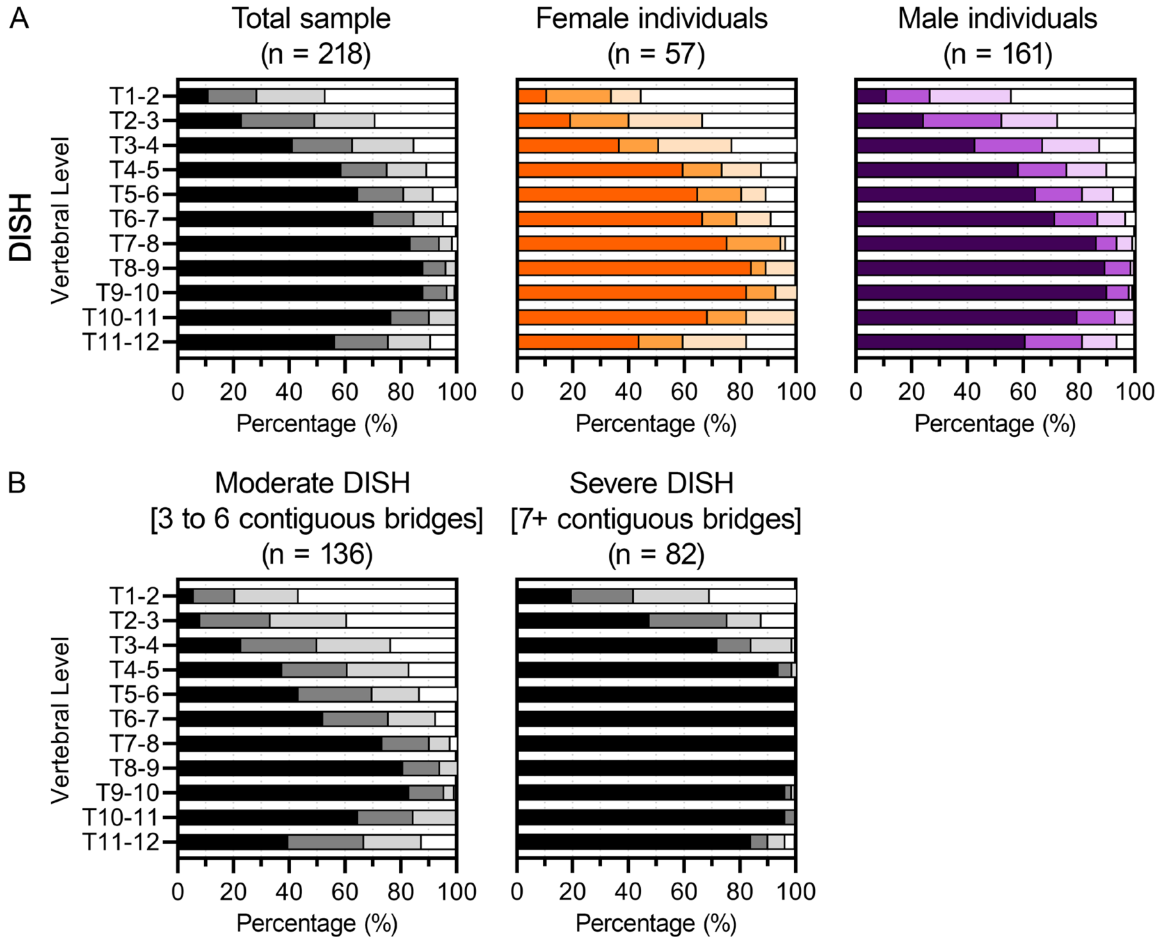

Figure 2.6. Imaging characteristics of DISH

A, Anatomical distribution of ectopic bridging in individuals meeting the criteria for diffuse idiopathic skeletal hyperostosis (n = 218 individuals, including: 57 female and 161 male). Darkest bars represent complete bridging (score of 3); medium bars represent near-complete bridging (score of 2); light bars represent anterior formations (score of 1); and white bars represent no bridging (score of 0). **B**, Visualization of the anatomical distribution of ectopic bridging in two subgroups: those presenting with 3 to 6 completed bridges and those with 7 to 11 complete bridges.

83, 44 to 104years) with complete bridges, potentially indicating a threshold to classify severe disease (**Figure 2.6B**). Eleven individuals showed complete bridging of all thoracic motion segments.

In addition to the regions of contiguous bridging that met the criteria for DISH, we noted heterogeneity in extent of ectopic bridging throughout the remainder of the thoracic spine (**Figure 2.5B&C**). At least one additional complete bridge (non-contiguous) was observed in 35.9% of individuals with DISH, involving up to four motion segments. Presentations included: a single motion segment with a complete bridge (52.7%); at least one site of two contiguous motion segments bridged (24.3%); two motion segments with complete bridges separated by at least one motion segment without a complete bridge (14.9%); or a combination of the above (8.1%). The frequency of these presentations was not affected by sex or age of individuals. Outside of regions meeting the criteria for DISH, incomplete bridging (bridge scores of 1 or 2) was detected in 74.6% of motion segments. Age and sex were not associated with incomplete bridging outside of regions of DISH. Of note, motion segments immediately adjacent to regions of DISH almost always displayed some form of ectopic mineral (89.4%). Furthermore, 53 individuals concurrently met the criteria for both DISH and early-phase DISH in distinct regions of the thoracic spine. The most common patterns of early-phase DISH were two contiguous complete bridges and one incomplete bridge (3-3-2: 41.5%) and three incomplete bridges (2-2-2: 34.0%) (**Figure 2.5B**).

2.5.5 Imaging characteristics of group without any phase of DISH

Features of ectopic spine mineralization detected in the without group may reflect the earliest presentations of DISH (**Figure 2.5D**). Few individuals (6.5% of group) displayed at least one motion segment with a complete bridge. Individuals with a complete bridge were more often male (1.6:1; p=.01) and older than those without any complete bridging (median age of 72, 27 to 103 years compared to 59.3 years; p<0.001). A single complete bridge was observed in 66 individuals and two distinct regions of complete bridging were observed in seven individuals. Typically, the number of motion segments with some form of ectopic mineral and at least one complete bridge was 5.2 ± 1.9 (range 2 to 10) (no significant age or sex difference). In contrast, 62.0% of individuals showed only incomplete bridging. There was no difference in the average number of motion segments with incomplete bridging between female and male individuals (3.8 ± 2.3, range 1 to 11). Lastly, no evidence of ectopic spine mineral was detected in 31.5% of individuals in this group.

2.6 Discussion

Historically, the diagnosis of DISH has been limited to advanced disease state and the continuum of imaging features remains poorly understood. In this study, we sought to identify DISH and early-phase DISH throughout the adult lifespan in a group of 1,536 Americans using thoracic spine imaging. Our analysis demonstrated the prevalence of DISH to be 14.2% (7.4% of female and 20.9% of male individuals), first detected at 40 years of age. Early-phase DISH was detected in 13.2% of the sample (10.4% of female and 15.8% of male individuals), starting at 35 years of age. While DISH and early-phase DISH were more common in male individuals, no striking differences in imaging features (i.e., pattern of mineral formation, anatomical location) were noted between sexes. These findings demonstrate a combined prevalence of 27.3% for DISH and early-phase DISH, with a striking 5.2-fold increase between individuals in their 30s and 40s during the time of anticipated initial onset in this population.

Our reported prevalence of DISH aligns with previous studies using trauma-related computed tomography imaging that indicated rates ranging from 6.9 to 19.5% (17, 23, 24, 26). Our analysis of computed tomography images found that 11.4% of female and 32.6% of male individuals over the age of 50 displayed imaging features consistent with DISH. In comparison, a study of chest radiographs from the same geographic region reported DISH in 15% of female and 25% of male individuals over the age of 50 (33). The different prevalence rates detected in the current study may be attributed to the improved sensitivity of computed tomography compared to X-ray in detecting features of DISH (14) or an increase in risk factors for DISH over the past 25 years (e.g., sedentary lifestyle, diet, and metabolic dysfunction). Further, the sex-related differences in DISH may be associated with different rates of disease progression, which could be affected by innate biological, biomechanical, or social factors. Such findings underscore the importance of including both sexes in studies of DISH, including those aimed at understanding the mechanisms underlying disease pathogenesis.

One novelty of the current study was the simultaneous investigation of early-phase DISH and DISH, throughout the adult lifespan. The finding that the youngest individuals identified with early-phase DISH and DISH were 35 and 40 years of age, respectively, was expected given that mineral formation is thought to be a slow process (28-30). We expected that a random sample would identify more individuals with early-phase DISH earlier in life compared to DISH than was the case. These findings suggest that refinement of the criteria for early-phase DISH is needed to reliably detect features earlier in the disease continuum. The value of reliably detecting early disease features is the potential increased prospective clinical observations across the continuum of DISH. Perhaps this is a limitation of the sample population used for the development of the early-phase criteria: only males over the age of 50 with images at least 2.5 years apart (29). It is likely that some presentations of ectopic bridging we detected in individuals that did not meet the criteria for either DISH or early-phase DISH represent the earliest stage(s) of DISH. Future studies to improve the characterization of the continuum of imaging features need to consider evaluating individuals before the age of 50 with repeated images at intervals of less than 2.5 years.

Findings from our study combining assessment of prevalence with detailed examination of ectopic mineral formation at the level of individual motion segments highlighted remarkable diversity in the imaging features of individuals within each disease group. These findings enable us to put forward two specific needs to advance the understanding and classification of the continuum of DISH pathogenesis. First, the widespread detection of ectopic mineral bridges outside the region meeting the diagnostic criteria for early-phase DISH or DISH suggests that evaluation of ectopic mineral formation across the entire thoracic spine may more robustly characterize presentations of DISH. Motion segments immediately adjacent to regions meeting the diagnostic criteria for DISH may provide insight on disease activity that is not considered in the current diagnostic criteria. A holistic strategy that classifies early-phase DISH based on imaging features of the whole spine may reduce the emphasis on contiguous motion segment involvement. For example, evaluation of the summed score of ectopic bridging, number of involved motion segments, and anatomical localization may reveal unique presentations of early-phase DISH or DISH. Classification of the continuum of DISH based on other imaging or physical features unique to DISH (e.g., structural appearance, volume of ectopic mineral, bone mineral density) may also have merit (4,5,34).

Second, our analysis of ectopic mineralization in individuals with DISH revealed complete bridging across an average of six contiguous motion segments, a value that exceeds the threshold for clinical diagnosis (2). Previous studies reported a similar average of 6.6 to 9.2 contiguous bridges in the spine of individuals with DISH (16, 17, 21, 23, 25). We question whether the diagnostic emphasis on three or more contiguous motion segments with complete bridging should be reconsidered to better capture distinct stages of DISH. For example, ectopic bridges spanning three to six contiguous motion segments may represent “moderate DISH,” while those spanning greater than six motion segments may represent “severe DISH.” We suspect that extending the criteria for DISH to better represent its continuum may strengthen future studies that evaluate the association between radiographic features and clinical symptoms and/or identify key points along the continuum or populations to introduce conservative therapies. Further studies are also required to investigate the continuum of DISH in the cervical and lumbar spine to assess the onset of mineral formation, its spatial progression, and associated impairments.

While our study was limited to a retrospective analysis of a cross sectional sample from one geographic region, our random sampling strategy (stratified on age and sex) improved the representativeness of the sample and eliminated sex-biases present in previous studies (4, 17, 20, 24, 26). We acknowledge that the population assessed in this study was limited to people with access to healthcare and is overrepresented by people that are "white," thereby limiting the generalizability of our findings to diverse populations. A recent prevalence study of DISH among "African-American" and "Caribbean-American" individuals reported a prevalence of 7.7% (23), which was lower than our findings in a primarily "white" population. Another limitation is our exclusive focus on the anterior thoracic spine and acknowledge that analysis of features throughout the spine and peripheral joints may elucidate additional important clinical features of DISH.

In conclusion, our findings demonstrate that DISH is a common musculoskeletal condition involving the thoracic spine of Americans and is prevalent across the adult lifespan beginning at 35 years of age in both sexes. Our findings suggest that more than one in three individuals over the age of 39 has imaging features consistent with early-phase DISH or DISH. We observed early-phase DISH throughout the thoracic spine and as such postulate that the current emphasis on contiguous motion segment involvement captures a diverse and likely incomplete group under the umbrella of "early-phase DISH." There is a need for research on the etiology, progression, and clinical implications of DISH prior to its detection in advanced presentations. Recognition of the full spectrum of this poorly understood disease may be an important step to improve early detection and identify factors associated with disease onset. Together this may lead to a better understanding of etiology and targets for the development of treatments.

2.7 References

1. Forestier J, Rotes-Querol J. Senile ankylosing hyperostosis of the spine. Annals of the Rheumatic Diseases 1950;9(4):321-30.

2. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology 1976;119(3):559-68.

3. Baraliakos X, Listing J, Buschmann J, et al. A comparison of new bone formation in patients with ankylosing spondylitis and patients with diffuse idiopathic skeletal hyperostosis: A retrospective cohort study over six years. Arthritis and Rheumatism 2012;64(4):1127-33.

4. Kuperus JS, Buckens CF, Šprem J, et al. The natural course of diffuse idiopathic skeletal hyperostosis in the thoracic spine of adult males. Journal of Rheumatology 2018;45(8):1116-23.

5. Fournier DE, Norley CJD, Pollmann SI, et al. Ectopic spinal calcification associated with diffuse idiopathic skeletal hyperostosis (DISH): A quantitative micro-CT analysis. Journal of Orthopaedic Research 2019;37(3):717-26.

6. Utsinger PD. Diffuse idiopathic skeletal hyperostosis. Clinics in Rheumatic Diseases 1985;11(2):325-51.

7. Katzman WB, Huang MH, Kritz-Silverstein D, et al. Diffuse idiopathic skeletal hyperostosis (DISH) and impaired physical function: The Rancho Bernardo study. Journal of the American Geriatrics Society 2017;65(7):1476-81.

8. Harlianto NI, Kuperus JS, Mohamed Hoesein FAA, et al. Diffuse idiopathic skeletal hyperostosis of the cervical spine causing dysphagia and airway obstruction: An updated systematic review. The Spine Journal 2022;22(9):1490-503.

9. Murakami Y, Mashima N, Morino T, et al. Association between vertebral fracture and diffuse idiopathic skeletal hyperostosis. Spine 2019;44(18):E1068-74.

10. Okada E, Shimizu K, Kato M, Fukuda K, Kaneko S, Ogawa J, et al. Spinal fractures in patients with diffuse idiopathic skeletal hyperostosis: Clinical characteristics by fracture level. Journal of Orthopaedic Science 2019;24(3):393-9.

11. Lantsman DC, Barkay G, Friedlander A, et al. Whole spine CT scan for the detection of acute spinal fractures in diffuse idiopathic skeletal hyperostosis patients who sustained low-energy trauma. Spine 2020;45(19):1348-53.

12. Guiot A, Estublier C, Gaude M, et al. Relationship between diffuse idiopathic skeletal hyperostosis and fragility vertebral fracture: A prospective study in older men. Rheumatology 2021;60(5):2197-205.

13. Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: Clinical features and pathogenic mechanisms. Nature Reviews Rheumatology 2013;9(12):741-50.

14. Hirasawa A, Wakao N, Kamiya M, et al. The prevalence of diffuse idiopathic skeletal hyperostosis in Japan – the first report of measurement by CT and review of the literature. Journal of Orthopaedic Science 2016;21(3):287-90.

15. Fujimori T, Watabe T, Iwamoto Y, et al. Prevalence, concomitance, and distribution of ossification of the spinal ligaments results of whole spine CT scans in 1500 Japanese patients. Spine 2016;41(21):1668-76.

16. Mori K, Kasahara T, Mimura T, et al. Prevalence of thoracic diffuse idiopathic skeletal hyperostosis (DISH) in Japanese: Results of chest CT-based cross-sectional study. Journal of Orthopaedic Science 2017;22(1):38-42.

17. Hiyama A, Katoh H, Sakai D, et al. Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) assessed with whole-spine computed tomography in 1479 subjects. BMC Musculoskeletal Disorders 2018;19(1):1-7.

18. Kim BS, Moon MS, Yoon MG, et al. Prevalence of diffuse idiopathic skeletal hyperostosis diagnosed by whole spine computed tomography: A preliminary study. Clinics in Orthopedic Surgery 2018;10(1):41-6.

19. Hirasawa A, Robinson Y, Olerud C, et al. Regional differences in diffuse idiopathic skeletal hyperostosis. Spine 2018;43(24):E1474-E8.

20. Liang H, Liu G, Lu S, et al. Epidemiology of ossification of the spinal ligaments and associated factors in the Chinese population: A cross-sectional study of 2000 consecutive individuals. BMC Musculoskeletal Disorders 2019;20(1):1-12.

21. Adel H, Khan SA, Adil SO, et al. CT-based evaluation of diffuse idiopathic skeletal hyperostosis in adult population; Prevalence, associations and interobserver agreement. Journal of Clinical Densitometry 2020;23(1):44-52.

22. Auðunsson AB, Elíasson GJ, Steingrímsson E, et al. Diffuse idiopathic skeletal hyperostosis in elderly Icelanders and its association with the metabolic syndrome: The ages-Reykjavik study. Scandinavian Journal of Rheumatology 2021;50(4):314-8.

23. Yoshihara H, Nadarajah V, Horowitz E. Prevalence and characteristics of thoracic diffuse idiopathic skeletal hyperostosis in 3299 black patients. Scientific Reports 2021;11(1).

24. Ahmed O, Ramachandran K, Patel Y, et al. Diffuse idiopathic skeletal hyperostosis prevalence, characteristics, and associated comorbidities: A cross-sectional study of 1815 whole spine CT scans. Global Spine Journal 2022 published on 26 October 2022. doi: 10.1177/21925682221136844

25. Ikuma H, Hirose T, Nakamura D, et al. The prevalence and characteristics of diffuse idiopathic skeletal hyperostosis (DISH): A cross-sectional study of 1519 Japanese individuals. Diagnostics 2022;12:1088

26. Singh NA, Shetty AP, Jakkepally S, et al. Ossification of posterior longitudinal ligament in cervical spine and its association with ossified lesions in the whole spine: A cross-sectional study of 2500 CT scans. Global Spine Journal 2023;13(1):122-32.

27. Tee DAG, Huang T-Y, Lai C-Y, et al. The utilization of single photon emission computed tomography/computed tomography (Spect/Ct) for detecting early-phase diffuse idiopathic skeletal hyperostosis. International Journal of Health Medicine and Current Research 2023; 26 (4):1-5.

28. Yaniv G, Bader S, Lidar M, et al. The natural course of bridging osteophyte formation in diffuse idiopathic skeletal hyperostosis: Retrospective analysis of consecutive CT examinations over 10 years. Rheumatology 2014;53(11):1951-7.

29. Kuperus JS, Oudkerk SF, Foppen W, et al. Criteria for early-phase diffuse idiopathic skeletal hyperostosis: Development and validation. Radiology 2019;291(2):420-6.

30. Murakami Y, Morino T, Hino M, et al. Progression of ossification of the anterior longitudinal ligament associated with diffuse idiopathic skeletal hyperostosis by age: A study of computed tomography findings over 5 years. Global Spine Journal 2021;11(5):656-61.

31. Rocca WA, Yawn BP, St Sauver JL, et al. History of the Rochester Epidemiology Project: Half a century of medical records linkage in a US population. Mayo Clinical Proceedings 2012;87(12):1202-13.

32. Oudkerk SF, de Jong PA, Attrach M, et al. Diagnosis of diffuse idiopathic skeletal hyperostosis with chest computed tomography: Inter-observer agreement. European Radiology 2017;27(1):188-94.

33. Weinfeld RM, Olson PN, Maki DD, et al. The prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in two large American Midwest metropolitan hospital populations. Skeletal Radiology 1997;26(4):222-5.

34. Kuperus JS, Samsour L, Buckens CF, et al. Bone mineral density changes over time in diffuse idiopathic skeletal hyperostosis of the thoracic spine. Bone 2018;112:90-6.

35. Nishida N, Jiang F, Ohgi J, et al. Biomechanical analysis of the spine in diffuse idiopathic skeletal hyperostosis: Finite element analysis. Applied Sciences (Switzerland) 2021;11(19):1-13.

Chapter 3

Thoracic Spine Computed Tomography Scans and Diffuse Idiopathic Skeletal Hyperostosis: A Retrospective Study of Radiology Documentation

Authored by Dale E. Fournier, Andrew E. Leung, Cheryle A. Séguin, and Michele C. Battié.

3.1 Co-authorship statement

Dale E. Fournier contributed to study design with MCB. Dale E. Fournier performed data collection, analysis, and illustrations. AEL contributed clinical expertise. Manuscript was written by Dale E. Fournier with suggestions from MCB and critically revised by AEL and CAS.

3.2 Introduction

DISH is a musculoskeletal condition characterized by flowing mineralization along the anterolateral aspect of four contiguous vertebrae with preserved intervertebral disc height and lack of erosions, sclerosis, or ankylosis in the apophyseal or sacro-iliac joints (1) (**Figure 3.1**). DISH occurs throughout the spine. It is prevalent in 14% of adults and increases with advanced age (affecting one third of males 50+ years) (2). Histological investigation has revealed features of dystrophic calcification and heterotopic ossification (3); however, the etiology is unknown and its clinical consequences remain controversial. Routine and accurate identification of DISH on spine imaging may be key to advancing knowledge of the condition. The purpose of this study was to evaluate reporting of DISH in radiology reports.

3.3 Material and Methods

A retrospective, observational study was conducted with Health Insurance Portability and Accountability Act compliance and Institutional Review Board approval (20-000640). The prevalence of DISH was previously investigated using thoracic computed tomography scans from 1995-2019 in Minnesota, USA (2). All individuals with thoracic computed tomography scans acquired from previous medical care were identified by procedural codes (72128-30). Age- and sex-stratified random sampling was used to select 100 females and 100 males per decade—starting at 20 years—without restriction on race, health status, or indication.

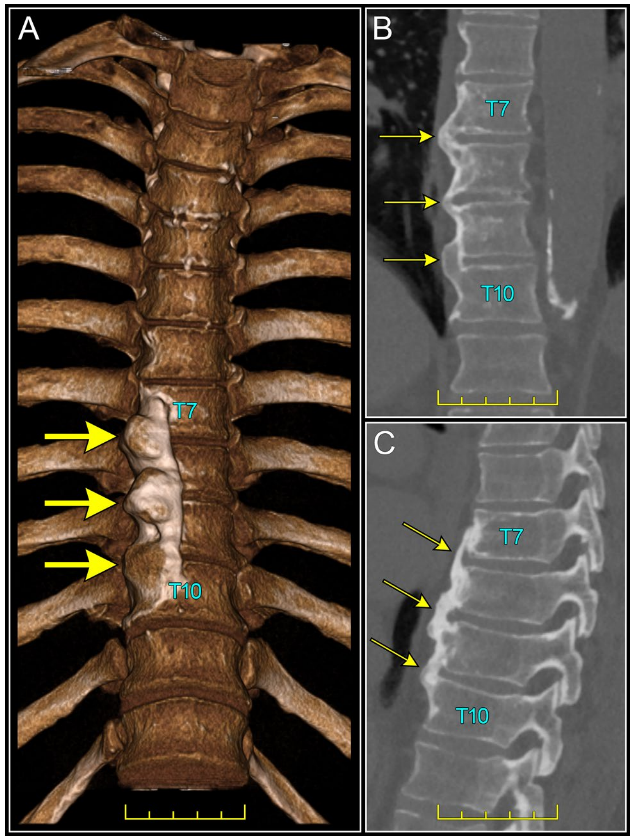

Figure 3.1. Representative clinical computed tomography images of a 69-year-old male individual with DISH that was documented in the radiology report

A, Three-dimensional rendering of the thoracic spine, anterior view. Yellow arrows indicate complete bridges required for the diagnosis of DISH. Non-contrast computed tomography images (**B**, coronal view) and (**C**, sagittal view) of the same representative thoracic spine shows ectopic bridging from T7–10. Scale bars indicate 5 cm. Diagnosis of DISH was determined by Resnick and Niwayama’s radiographic criteria developed in 1976: i) flowing ossification and hyperostosis along four vertebrae; ii) normal or mild decrease in intervertebral disc height in involved regions; and iii) absence of apophyseal or sacro-iliac joint erosions, sclerosis, or bony ankylosis.

Images were evaluated as previously reported (Chapter 2), which included using the established diagnostic criteria for DISH (1). Afterwards, indication for imaging was recorded and the associated radiology reports were screened with an a priori list of descriptors related to DISH and imaging features of ectopic bridging.

3.3.1 Statistical Methods

Data were collected from all included individuals. Chi-square test and logistic regression were performed using SPSS Statistics (Version 29.0, IBM Corp., Armonk, New York).

3.4 Results

Of 1,600 individuals evaluated, 4% were excluded because of anatomical deformity or image concerns, resulting in 1,536 individuals analyzed (50% males, 85% white, 80% trauma-related indication). The radiology reports directly referenced DISH in 24% of 218 individuals identified with the condition (**Figure 3.2**). Radiologists' reporting of DISH was greater in instances of moderate DISH (3-6 contiguous bridges) than severe DISH (7+ contiguous bridges) ($\chi2[1]=6.53$, $p=.01$). Over 70% of computed tomography scans were from 2013-2019, during which the probability of accurately reporting DISH improved annually (OR=1.31; 95% CI: 1.04, 1.63; $p=.02$) to a high of 34.6% in 2019. Imaging features of ectopic bridging were described in 37% of reports in lieu of DISH.

3.6 Discussion

Our study demonstrates substantial underreporting of DISH in a sample of adults referred for spine computed tomography scans. It is understood that the focus of reporting for trauma indications is acute injuries and less for chronic conditions. However, features of ectopic bridging were routinely documented while DISH was infrequently reported where

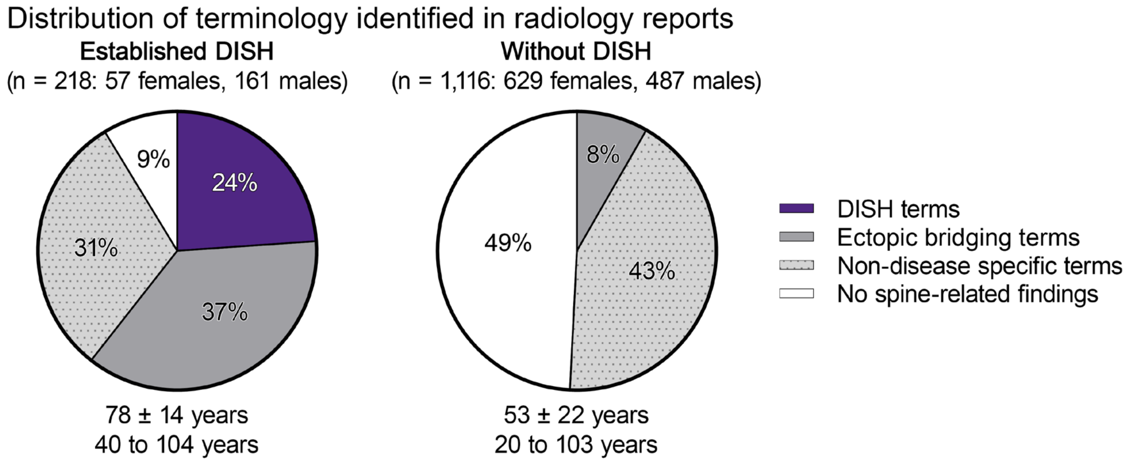

Figure 3.2. Distribution of terminology identified from the radiology report associated with each computed tomography scan

Data are expressed as a percentage for each group studied (with and without DISH). Established DISH is based on meeting Resnick and Niyawama's diagnostic criteria. Purple areas indicate DISH-related terminology: e.g., diffuse idiopathic skeletal hyperostosis, vertebral ankylosing hyperostosis, calcification, ossification of the anterior longitudinal ligament. Darker grey areas indicate ectopic bridging terms: e.g., osteophytes, bridging, ankylosis, syndesmophytes. Light grey areas indicate non-disease specific terms: e.g., degenerative, spondylotic, or hypertrophic changes. White areas indicate no mention of imaging features related to abnormal mineralization of the spine. Below each chart is the mean age, standard deviation, and range in years of individuals included in the group.

the condition was present. Greater awareness of DISH as a clinical entity in radiology reporting is warranted given the opportunity to advance knowledge of this common enthesopathy, for which the relationship between imaging features and clinical symptoms is poorly understood.

We acknowledge that despite using methods to ensure representativeness of the population with spine computed tomography scans, the radiology reports from one geographical region may not reflect the standards of practice elsewhere or the entire specialty. Yet, the findings do suggest an important opportunity to enhance the value of spine imaging reporting. For example, improved awareness of DISH may be invaluable for health care providers to prevent adverse outcomes, such as incidental fractures resulting in neurological deficits (4) or complications during medical procedures (5,6).

Furthermore, accurate reporting of DISH may yield important clinical observations and research that leads to new knowledge of disease features, etiology, clinical symptoms, as well as innovative medical or non-medical interventions. Ultimately, radiology is uniquely positioned to advance the field of DISH research and patient care.

3.7 References

1. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology 1976;119(3):559-568.

2. Fournier DE, Leung AE, Battie MC, Seguin CA. Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) and early-phase DISH across the lifespan of an American population. Rheumatology 2023. doi: 10.1093/rheumatology/kead362

3. Fournier DE, Kiser PK, Beach RJ, et al. Dystrophic calcification and heterotopic ossification in fibrocartilaginous tissues of the spine in diffuse idiopathic skeletal hyperostosis (DISH). Bone Res 2020;8(1).

4. Hartel MJ, Seidel U, Iselin L, et al. Partial tetraplegic syndrome as a complication of a mobilizing/manipulating procedure of the cervical spine in a man with Forestier's disease: A case report. J Med Case Rep 2011;5(529).

5. Ihara M, Ueno A, Tsuda Y, et al. A case of repeated occlusion in the common iliac artery due to an unexpected stent deformation. Cardiovasc Interv Ther 2015;30(2):162-167.

6. Young D, Saxby K, Beard M, et al. Acute bilateral vocal cord paralysis (BVCP) in a patient with undiagnosed diffuse idiopathic skeletal hyperostosis (DISH). Chest 2021;160(4):890A-891A.

Chapter 4

Spatiotemporal Changes in Imaging Features Associated with Diffuse Idiopathic Skeletal Hyperostosis (DISH)

Authored by Dale E. Fournier, Michele C. Battié, and Cheryle A. Séguin.

4.1 Co-authorship statement

Dale E. Fournier lead study design with contributions from MCB and CAS. Dale E. Fournier performed data collection, analysis, and illustrations. Manuscript was written by Dale E. Fournier with suggestions from CAS and MCB.

4.2 Chapter summary

The purpose of our study was to characterize spatiotemporal features of disease progression over time using repeated computed tomography scans of the thoracic spine from people with DISH, early-phase DISH, and those not meeting either criterion.

A retrospective study was designed in collaboration with the Rochester Epidemiology Project to evaluate completeness of ectopic bridging and disease status over an average of 2.7 years (range from 0.2 to 15.0 years) with 83 female and 74 male individuals.

Over fifteen percent of individuals displayed changes in imaging features over time that resulted an adjusted diagnosis along the continuum of DISH. Early-phase DISH is marked by new involvement of previously unaffected motion segments, estimated to occur over 2.1 years. Whereas, advanced presentations of DISH are marked by increased prevalence of complete bridging (average 2 of 3 available motion segments), estimated to occur over 2.6 to 2.9 years. Localized nodules of ectopic mineralization external and within the intervertebral disc were regularly observed in early-phase DISH.

This is the first characterization of spatiotemporal features across all phases of DISH, indicating that progression of DISH is characterized by distinct features at different phases along the disease continuum. Localized nodules of mineralization the spinal ligaments and within the intervertebral disc are coincident with early phases of the disease and may serve a key factor in the pathogenesis of DISH.

4.3 Introduction

DISH is a non-inflammatory enthesopathy of the spine (1) that affects an estimated 14% of adult Americans and over one third of males of 50 years (2). The clinical presentation of DISH can include physical dysfunction (3-5), obstruction of the airway (6), or compromised neural tissues (7-11). The rigid spine associated with DISH also increases risk for vertebral fractures from low-energy forces (12-15). DISH is more prevalent in males of advanced age, but the underlying etiology is unknown (16).

The diagnosis of DISH is based on Resnick and Niwayama's radiographic criteria of ectopic mineral bridges that connect four contiguous vertebrae of the spine with preserved intervertebral disc height and absence of bony ankylosis of the apophyseal or sacro-iliac joints in the involved areas (17). The severity of DISH can be further categorized based on the number of contiguous bridges detected (2). These mineral formations present heterogeneously as osteophyte-like outgrowths and/or flowing bands of mineralized tissue (18-21).

Early-phase DISH is categorized based on the assessment of completeness of ectopic bridging and the spatial relationship across three contiguous segments (22). The prevalence of early-phase DISH is reported to be 13% of adults with an average age of 73 years and slightly greater prevalence in male compared to female individuals (2).

This study sought to describe the spatiotemporal progression of ectopic mineralization in the thoracic spine by evaluating repeated computed tomography scans from individuals meeting the diagnostic criteria for DISH and early-phase DISH at the time of the most recent image from a cross-sectional patient population. We are the first to provide a detailed characterization of the change in imaging features of ectopic mineralization in the thoracic spine over time. We specifically focused on the continuum of DISH pathogenesis for individuals with early-phase DISH, moderate and severe DISH. We hypothesized that better understanding the progression of ectopic mineralization in the spine will elucidate unique clinical features of DISH and better inform on disease continuum.

4.4 Methods

4.4.1 Data source

Data was retrieved from the Rochester Epidemiology Project that collates individual's health information from various clinical encounters in Minnesota, United States (23, 24). Our study was approved by both Institutional Review Boards (20-000640; 008-OMC-20).

4.4.2 Study design and sample population

Computed tomography scans of the thoracic spine were retrospectively analysed from a cross-sectional patient population using data that was prospectively collected between 1995 and 2019 (2). Adults over the age of 19 years were searched for thoracic spine scans using procedural codes (72128-30). A minimum threshold of two months between scans was set to capture acute or chronic changes over time. There were no restrictions regarding sex, race, indication for imaging, or past medical history. Four distinct groups were identified based on the last image: those meeting Resnick and Niwayama's criteria for DISH (moderate = 3-6 contiguous bridges; severe =7+ contiguous bridges) (2,17), those meeting Kuperus and colleague's criteria for early-phase DISH (22), and those that did not meet either criterion (**Figure 4.1**). The data

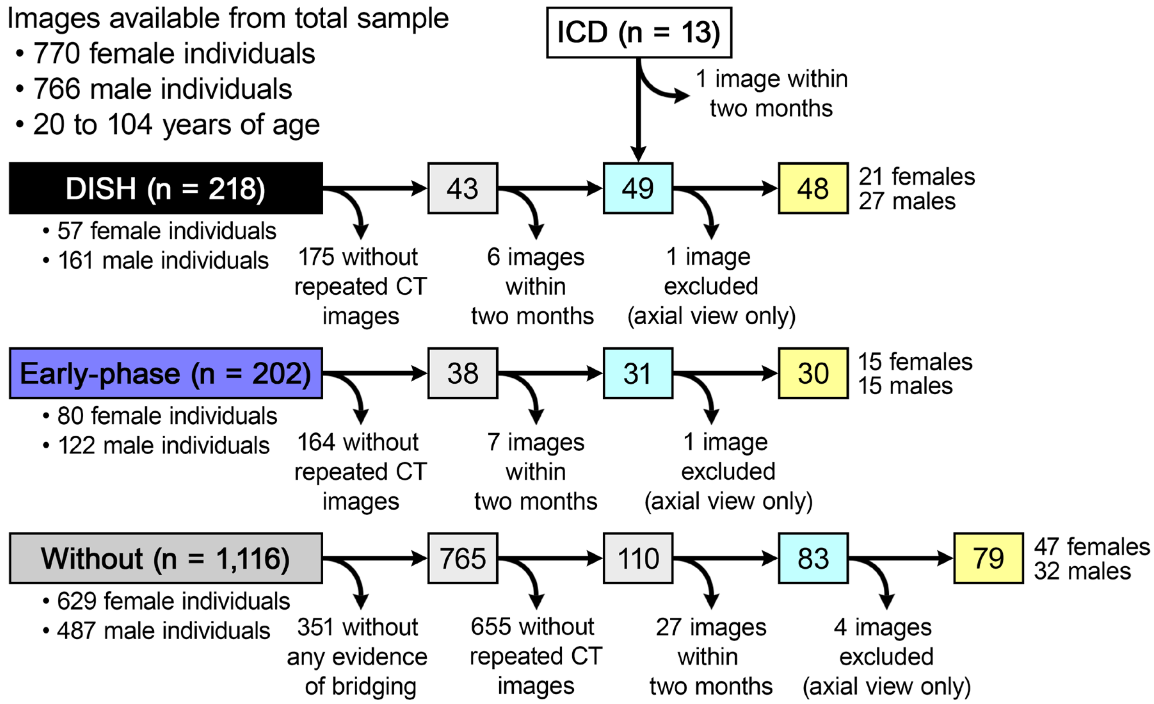

Figure 4.1. Flowchart of study sample from cross-sectional population

Groups were populated from previously established diagnosis of DISH, early-phase DISH, or those that did not meet either criterion. Individuals without repeated images or images less than two months apart were excluded. A search for DISH based on International Statistical Classification of Diseases and Related Health Problems (v.9 and 10) codes revealed a group of 13 individuals with multiple images that were included. The cyan boxes represent the number of individuals with multiple computed tomography images that were viewed. The yellow boxes represent the final number of individuals included in the study. Of which, thirteen motion segments from three individuals could not be evaluated because of limitations in field of view. Localized deformity was reason to exclude 27 motions segments from 15 individuals. Since unique motions segments excluded in one image were also excluded in repeated images from the same individual, a total of 64 motion segments from 18 individuals were removed (1.9% of all motion segments).

source was searched using International Statistical Classification of Diseases and Related Health Problems codes that represent DISH (v9: 721.6; v10: M48.1*), which identified an additional 13 individuals with repeated computed tomography images for inclusion (**Figure 4.1**). The last image from individuals with an ICD code for DISH was also evaluated to confirm DISH.

Image acquisition consisted of thoracic and thoracolumbar spine protocols with reported pixel resolutions ranging from 0.6 to 1.1 mm. QREADS Clinical Image Viewer (Version 5.14.0, Mayo Clinic) was used to evaluate the reconstructed sagittal and frontal views (consistent window of 2500 and level of 350). Primary analysis was the difference between the last and first computed tomography images available. The list of 163 individuals and their repeated images were randomized to reduce order bias during image evaluation; although, age and sex were known.

It was established a priori that images with significant deformity that disrupted anatomy would be excluded (e.g., intervertebral disc degeneration with fused motion segments, exaggerated kyphosis or scoliosis). Evidence of ankylosing spondylitis—differentiated based on thin band of ectopic mineralization and presence of zygapophyseal joint erosion or fusion—was also reason for exclusion. When a unique motion segment was excluded in one image, it was also excluded in any repeated images from the same individual.

4.4.3 Image evaluation

This study builds upon our previous work evaluating the continuum of imaging features observed in DISH (2). A validated scoring system was used to evaluate the completeness of ectopic bridging at the level of the individual motion segment; patterns of ectopic bridging were assessed to determined disease categorization. Intervertebral disc mineralization was recorded. Inter-rater reliability indicated substantial to excellent agreement between raters in the diagnosis and bridge scoring (Chapter 2.4.2).

4.4.4 Statistical methods

SPSS Statistics (Version 29.0, IBM Corp., Armonk, New York) was used for analysis. Ordinal bridge score data required nonparametric tests. Paired data was evaluated using Wilcoxon signed-ranked test for ordinal variables and McNemar tests for binary variables. Chi-squared and Fisher exact tests were used to evaluate differences between groups and sexes, and post-hoc testing was performed using adjusted standardized residuals and Bonferroni's multiple comparisons. Mann-Whitney U test and Kruskal Wallis pairwise test with Dunn's multiple comparisons were used to analyze differences between sexes and groups with quantitative data. Predictive modelling of changes over time was performed using logistic regression and fixed linear regression analysis.

4.5 Results

4.5.1 Sample characteristics

From a sample of 1,536 individuals, 163 were identified with repeated computed tomography scans of the thoracic spine and 157 were included in this study (**Figure 4.1**). Overall, 91.7% of the individuals were reported as "white." The most recent image was used to categorize individuals within the groups by disease status.

The predominate indication for computed tomography of the thoracic spine was physical trauma (76%: e.g., bodily injury, motor vehicle collision, or falls). Other indications are neurological reasons (11%), query of fracture (6%), surgical relevance (5%), or cancer screening and/or health follow up (2.2%). Between groups, the indication for imaging people with DISH was more associated with trauma compared to the other groups.

There was no difference in the time interval between scans by sex or groups. The average time between scans was 2.7 years and ranged from 0.2 to 15.0 years. At the time of the last image, individuals with DISH were significantly older than those in the without group (78 ± 14 years, range 44 to 104 compared to 68 ± 21 years, range 25 to 100; p=.03). No age or sex differences were noted between groups at the time of the first image.

4.5.2 Evaluation of repeated scans revealed spatiotemporal changes in ectopic spine mineralization

The continuum of DISH can be categorized based on criterion that distinguish early-phase DISH (22), DISH (17), and the severity of DISH (2). Progression along the continuum was observed in 15% of individuals without sex-related differences (**Figure 4.2A**). Individuals that changed disease categories were older than those that remained unchanged (80 ± 14 years compared to 70 ± 19 years; p=.02). Increased disease severity was seen in 16% of individuals from groups where severity could progress (without group, early-phase DISH, and moderate DISH). Decreased disease severity was observed in 4% of individuals. These were linked to spine surgery or injury between scans that may have disrupted contiguous ectopic bridging. In the timeframe assessed, no individuals progressed from the without group to DISH (moderate or severe) or vice versa.

The criteria for early-phase DISH are based on evaluation of ectopic mineral bridging at

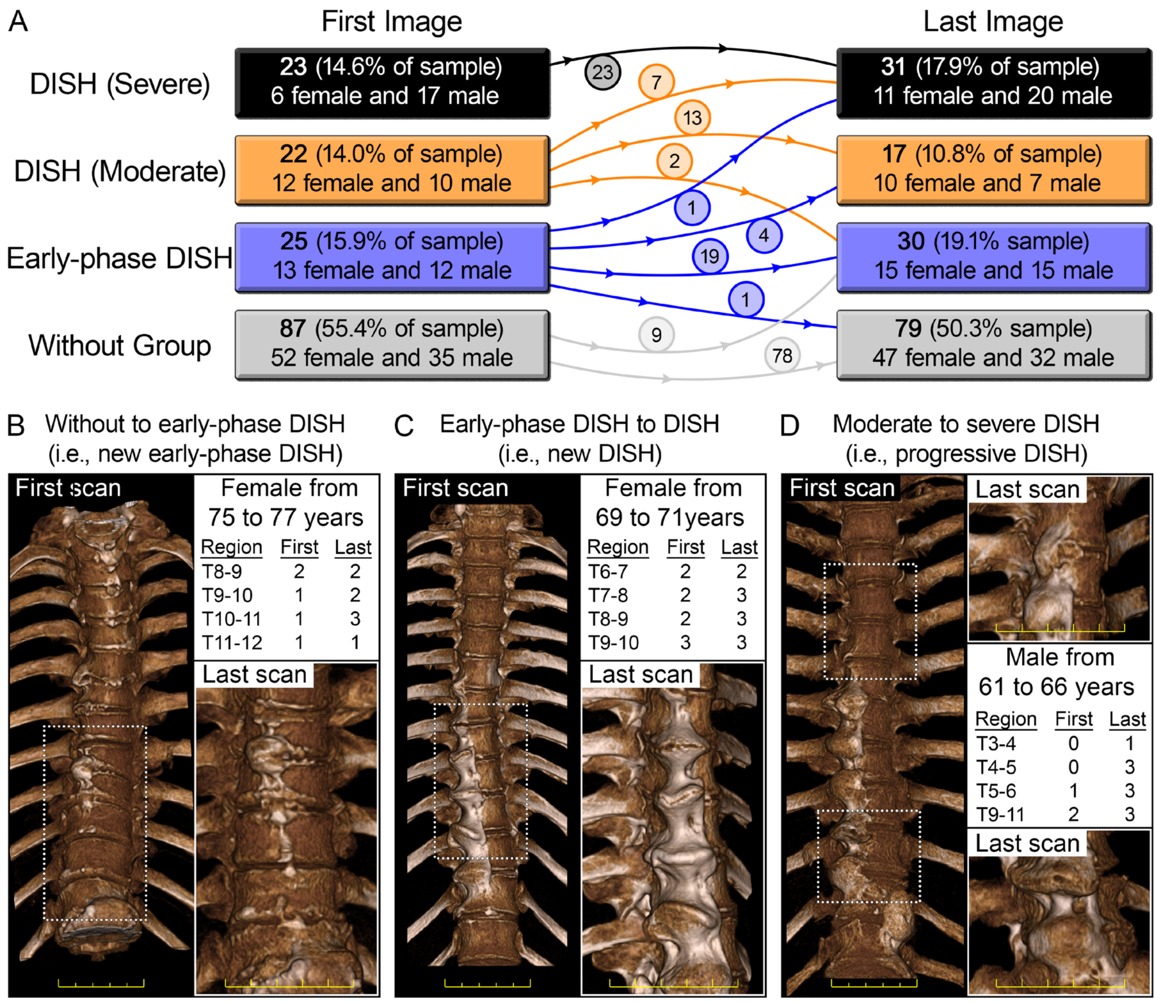

Figure 4.2. Changes in disease stage along the continuum of DISH over time with repeated scans.

A, Schematic representation of categorization of individuals based on DISH disease stage highlighting changes between first and last image. **B-D**, Three-dimensional renderings highlighting the changes in ectopic bridging over time from three unique individuals using 3D Slicer (Version 5.2.2.). Representative images of the thoracic spine showing regions associated with the progression from (**B**) without to early-phase DISH, (**C**) early-phase DISH to DISH, and (**D**) moderate to severe DISH. Inlays present the bridging score at specific motion segments associated with the first and last image for each individual. Scale bars represent 5 cm.

individual motion segments (scored as 0-3) and the spatial pattern of bridging across three contiguous motion segments (22). All possible patterns to fulfill the criteria for early-phase DISH were observed at least once in individuals that progressed from the without group to early-phase DISH (i.e., new early-phase DISH), with the most common being 3-2-3 and 3-2-2 (**Figure 4.2B**). When individuals progressed from early-phase DISH to either moderate or severe DISH (i.e., new DISH), the most common contiguous bridging patterns of early-phase DISH in the first image were 3-2-2, 3-3-2, and 2-2-2 (**Figure 4.2C**). Individuals that progressed from moderate to severe DISH (7 total) displayed an average increase of three contiguous bridges (first scan = 5, range 3-6; last scan = 8, range 7-10) (**Figure 4.2D**).

4.5.3 Changes in ectopic spine mineralization in individuals that did not meet the criterion for DISH

Despite categorization to the without group, an average of 3 motions segments per individual (range 0-11) displayed evidence of ectopic spine bridging in the first scan in the without group. In the last scan, almost half of individuals (43.6%) displayed at least one region of three contiguous motion segments with some evidence of ectopic mineralization. More complete bridging was detected in the last scan, which involved 11.5% of individuals and only 1.3% of motion segments. Over time, new involvement of at least one motion segment with ectopic spine mineralization was seen in 56.4% of individuals. Based on the current data set, regression analysis predicts that ectopic mineral formation at a new motion segment in the without group occurs every 5.0 years. In contrast, progressive changes in bridge score of previous affected regions (noted in 20.8% of individuals) was predicted to occur over an average of 2.4 years.

4.5.4 Characterization of changes over time associated with early-phase DISH

In the group of 30 individuals meeting the criteria for early-phase DISH in the last scan, the average number of motion segments per individual with ectopic mineralization increased between scans from 8 to 9 (p=.07). There was a significant increase in the severity of bridging scores between scans (**Figure 4.3A**).

Analysis of early-phase DISH was studied in three subgroups: new early-phase DISH (early-phase detected on the last scan only), unchanged early-phase DISH (detected on both scans), and new DISH (early-phase DISH on the first scan, DISH on the last scan).

We first characterized individual motion segments where new ectopic bridging was detected (i.e., present in last but not first scan). Individuals that progressed to new early-phase DISH showed the highest proportion of individual motion segments with new ectopic mineralization (average: 3 of 5 motion segments) compared to individuals with unchanged early-phase DISH diagnosis (average: 1 of 2 motion segments) or those with new DISH (average: 0.5 of 2 motion segments). Using linear regression analysis, the predicted time for ectopic mineralization of a previously unaffected motion segment in new early-phase DISH, unchanged early-phase DISH, and new DISH are 2.1, 5.8, and 3.1 years, respectively (**Figure 4.3B**). Of note, individuals with new early-phase DISH and unchanged early-phase DISH showed the greatest heterogeneity in bridge scores of the newly involved motion segments compared to individuals with new DISH (**Figure 4.3C**).

The progression in severity of bridge scores over time was next assessed in motion segments that displayed ectopic mineralization in the first image. Over half (55.9%) of

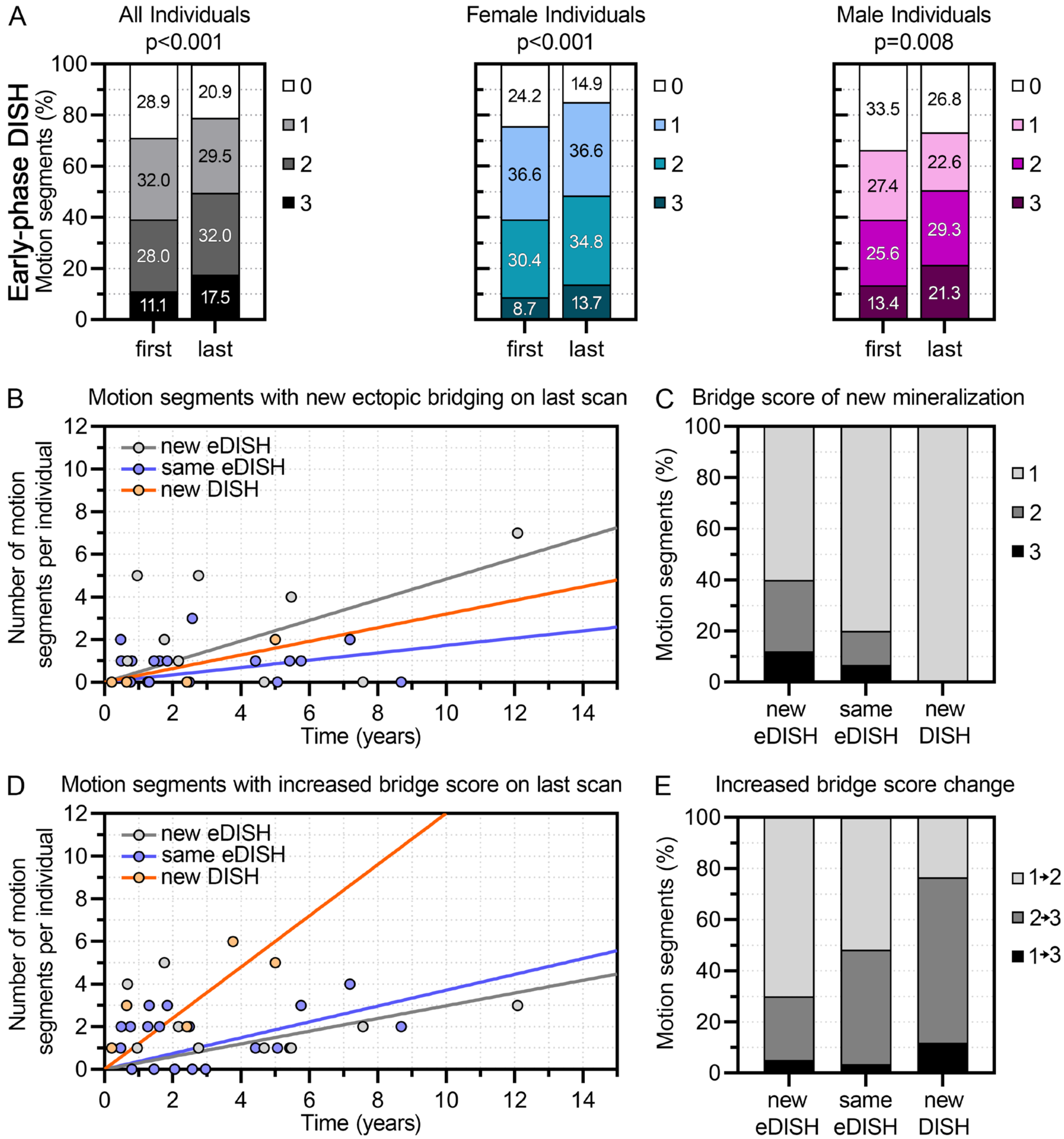

Figure 4.3. Quantitative analysis of changes associated with early-phase DISH

A, The distribution of ectopic mineralization of the thoracic spine in individuals that met the criteria for early-phase DISH in the last image compared to bridging score from the same individual in the first image. Legend indicates bridge score. **B**, Graph displays the extent of new involvement relative to time. Fixed linear regression analysis enabled predicative estimates per year. **C**, Distribution of bridge score in newly involved regions of individuals with new DISH, or unchanged and new early-phase DISH. **D**, Graph displays the number of motion segments with a change in bridge score relative to time. Fixed linear regression analysis enabled predicative estimates per year. **E**, Distribution of bridge scores in involved regions of individuals with new DISH, or unchanged or new early-phase DISH.

motion segments showed no change in bridge score in the last image. When a change in bridge score was observed, it was most often associated with increased bridging as opposed to reduced bridging (66% compared to 34% of motion segments). Increased bridge score was noted more in individuals with new early-phase DISH (average: 2 of 5 motion segments) and new DISH (average: 3 of 7 motion segments) compared to unchanged early-phase DISH (average: 2 of 7 motion segments). Linear regression analysis predicts that the time associated with increased bridging at one motion segment in new early-phase DISH, unchanged early-phase DISH, and new DISH are 3.4, 2.7, and 0.83 years, respectively (**Figure 4.3D**). A one unit change in bridge score was detected in 93.9% of motion segments that changed (**Figure 4.3E**). Individuals with new DISH had more motion segments that developed complete bridges compared to individuals with new or unchanged early-phase DISH (64.7% compared to 25.0% and 44.8%, respectively).

4.5.5 Characterization of changes over time associated with progression of DISH severity

Changes in ectopic mineralization over time were characterized in individuals with DISH at the first image. Three subgroups were established: unchanged moderate and severe DISH (same status on both scans) and progressive DISH (moderate DISH in the first scan, severe DISH in the last scan). Four individuals (two female and two male) displayed complete bridging of all motion segments in both images and as such were excluded from analysis. In the first image, 51.3% of individuals showed moderate DISH (three to six contiguous bridges) and 48.7% showed severe DISH (seven or more contiguous bridges). On average, 10 of 11 motion segments from individuals with DISH displayed ectopic bridging (9 of 11 in moderate DISH and 10 of 11 in severe DISH). In the last image, fewer near-complete bridges (p=.05) and more complete bridges (p=.03) were observed compared to the first image (**Figure 4.4A**). When stratified by sex, female individuals showed a greater increase in complete bridges in the last image compared to the first image (p=.06) whereas males did not (p=.19). Similar to changes in early-phase DISH, it was less common for bridge scores to increase more than one unit (two units = 15.7 %, three units = 5.9%).

New ectopic bridging at previously unaffected regions was seen in 48.0% of individuals with DISH and involved almost one third (31.6%) of available motion segments (**Figure 4.4B**). The average number of newly involved motion segments was slightly greater among individuals that progressed from moderate to severe DISH (average: 0.8 of 2 motions segments) compared to individuals that did not change disease categories (unchanged moderate DISH, average: 0.6 of 3 and unchanged severe DISH, average: 0.60 of 1 motion segments). Estimation using linear regression analysis predicted that mineralization of a new motion segment in individuals with progressive DISH and unchanged moderate or severe DISH occurs over 4.5, 3.9, and 6.1 years, respectively.

The progression of ectopic bridging in previously involved regions was observed in all individuals with progressive DISH, and 84.6 % of individuals with unchanged moderate DISH and 57.9% of individuals with unchanged severe DISH (**Figure 4.4C**). On average, 2 of 3 motion segments showed increase bridge scores in individuals that moved from moderate to severe DISH. Increased bridge score was seen in 1 of 4 and 0.5 of 2 available motion segments in those with unchanged moderate and severe DISH, respectively.

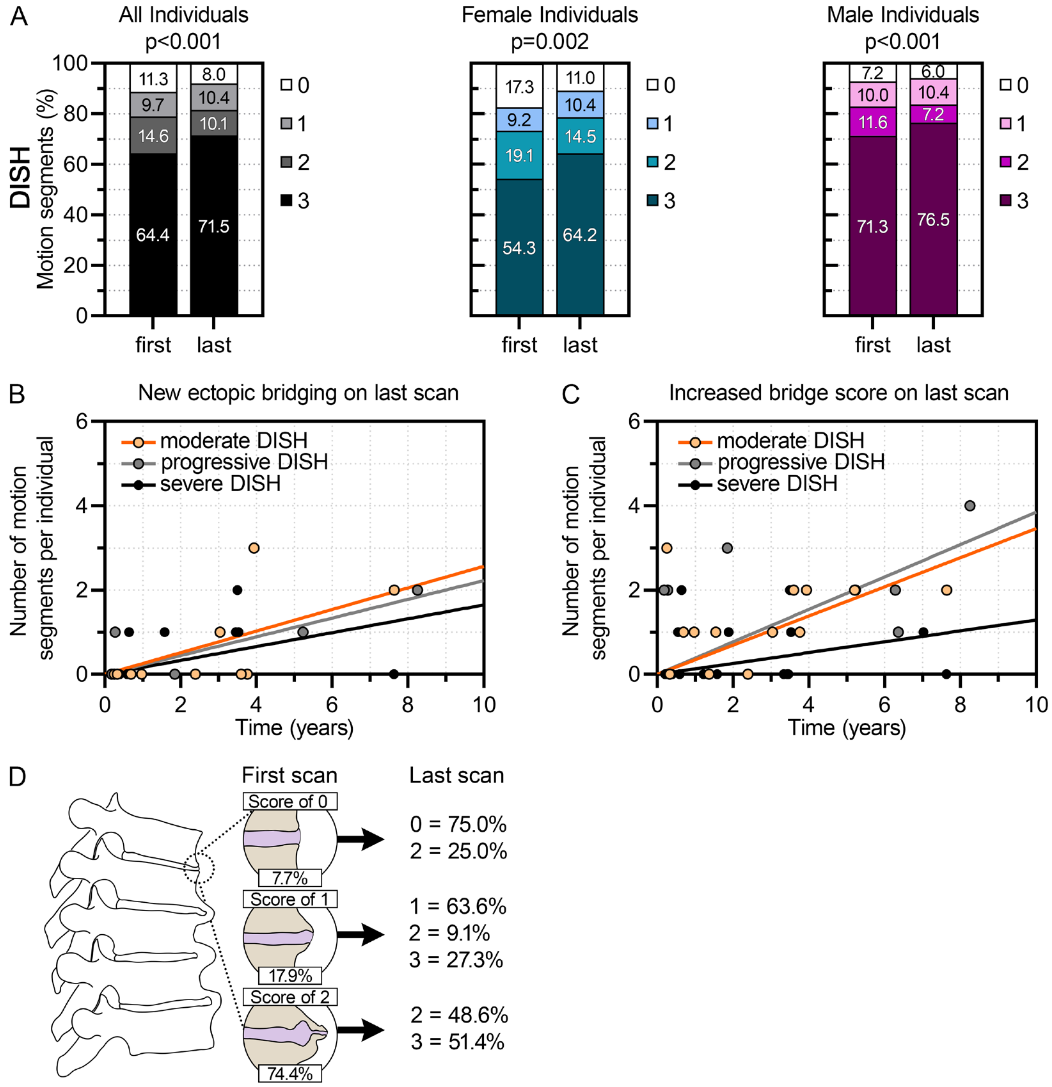

Figure 4.4. Quantitative analysis of changes associated with moderate to severe DISH

A, The distribution of ectopic bridge scores for motion segments of the thoracic spine in individuals that met the criteria for DISH in both scans, comparing bridges score from the same individual in the first image. Legend indicates bridge score. **B**, Graph displays the number of motion segments in each individual with mineralization present in only the last image relative to time. **C**, Graph displays the number of motion segments in each individual with increased bridge scores at the last image relative to time. Graphs are coded based on the diagnostic criteria for each individual (unchanged moderate DISH, progression from moderate to severe DISH, unchanged severe DISH). Fixed linear regression analysis used to predict the rate of new bridge formation or bridge progression. **D**, Visualization of the bridge scores at the motion segment adjacent to regions of contiguous bridging meeting the diagnostic criteria for DISH at the first and last image. Percentages are the number of immediately adjacent motion segments in the last scan that maintained the same bridge score or increased in bridge score compared to the first scan.

Linear regression analysis predicted that the time for increased bridge score at one motion segment in progressive DISH and moderate DISH is 2.9 and 2.6 years, whereas severe DISH is 7.8 years.

We specifically analyzed motion segments immediately adjacent to regions of contiguous bridging meeting the diagnostic criteria for DISH to assess progression of contiguous mineralization (**Figure 4.4D**). In the first image, 39 individuals with DISH displayed a motion segment with an incomplete bridge score immediately superior to the region of contiguous bridging. In the adjacent region, no bridge was observed in four individuals, early bridging in seven individuals, and near-complete bridging in 28 individuals. Nearly half (41.6%) of these regions displayed an increase in bridge score of the adjacent motion segment on the last scan compared to the first, with complete bridging observed in 41.0%. The occurrence of progression to a complete bridge in the superior motion segment was higher in individuals that progressed from moderate to severe DISH (55.6%) compared to unchanged moderate and severe DISH (38.5% and 31.6%, respectively). The region of contiguous bridging in the group with progressive DISH increased by an average of three contiguous bridges (range from one to five). Individuals with DISH in both images displayed minimal new involvement (0 to 3 motion segments) between images.

Logistic regression analysis at the level of the motion segment suggests variables that predict involvement with ectopic mineralization. Diagnosis and age at the first image, as well as time between images largely influenced the odds of new involvement or progressive changes (**Table 4.1**). Of note, sex was not a significant predictor.

Table 4.1. Logistic regression analysis for variables associated with ectopic mineralization at the level of motion segments

Variables	New Involvement (n=733)			Progressive Bridge Score (n=919)		
	OR	95% CI	p value	OR	95% CI	p value
Age* (in years)	1.00	.99, 1.01	.158	.98	.97, 1.00	.028
Sex						
- Female	1			1		
- Male	.76	.51, 1.14	.185	1.04	.67, 1.62	.870
Diagnosis*						
- Without						
- Early-phase	1			1	1.42, 4.09	
DISH	1.86	.98, 3.52	.057	2.41	1.87, 6.78	.001
- Moderate DISH	1.27	.59, 2.72	.536	3.56	1.85,	<0.001
- Severe DISH	4.94	1.65, 14.84	.004	4.68	11.80	.001
Diagnosis						
- Unchanged	1			1		
- Changed	3.92	2.25, 6.82	<0.001	5.41	3.23, 9.05	<0.001
Scan Interval						
(in years)	1.08	1.01, 1.15	.025	1.13	1.04, 1.22	.004

*collected from the time of the first computed tomography scan of the thoracic spine; CI, confidence interval; DISH, diffuse idiopathic skeletal hyperostosis; OR, odds ratio.

4.5.6 Localized nodules of ectopic mineralization within connective tissues of the spine

Distinct from ectopic bridging of vertebral bodies, isolated mineralized nodules were observed in proximity to the intervertebral disc, previously described as "nodular soft-tissue calcification" (22) (**Figure 4.5A**). Localized mineralized nodules were detected in 63.7% of individuals in the first image and 61.8% of individuals in the last image, corresponding to 14.2% of motion segments in the first image and 13.4% in the last image. No sex differences were reported. We assessed the prevalence of these formations based on location: i) connective tissues external to intervertebral disc (i.e., anterior longitudinal ligament) or ii) within the anulus fibrosus. Stratification based on localization revealed that mineralized nodules external to the intervertebral disc decreased in prevalence from 40.1 to 33.1% of individuals between images (p=.11). In contrast, a significant increase in the prevalence of anulus fibrosus nodules was observed from 39.5 to 49.0% of individuals between images (p=.03).

We assessed the relationship between localized nodules and the continuum of DISH. In the first scan, localized nodules were most often detected and more abundant in individuals early in the disease continuum (**Figure 4.5B, C**). Mineralization external to the intervertebral disc was most often associated with a bridge score of 1 (53.6%), in part because the presence of localized nodules adjacent to the intervertebral disc meets the criteria for a bridge score of 1 (20) (**Figure 4.5D**).

Lastly, we evaluated the presence of localized nodules over time. Slightly more nodules were detected in both images compared to nodules that were new (present only in the last

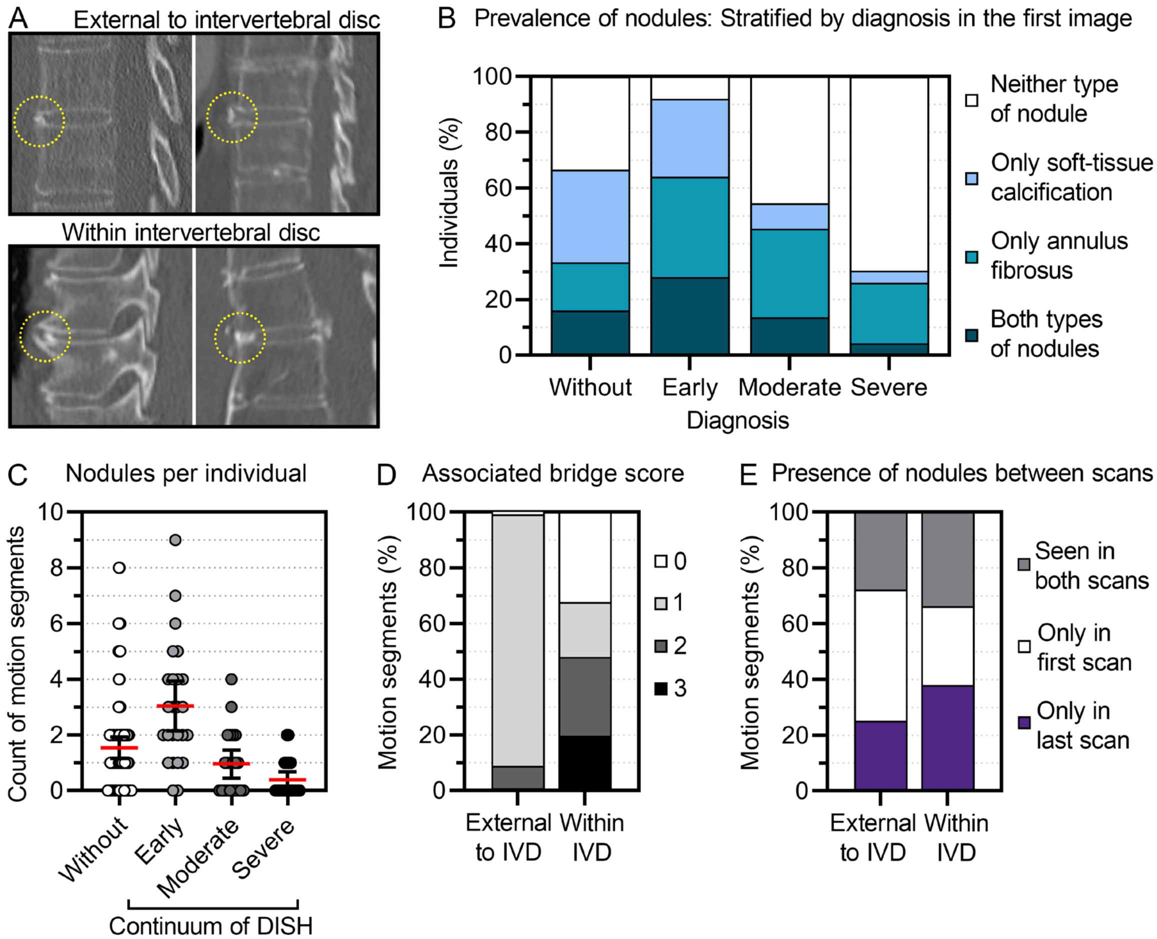

Figure 4.5. Prevalence and association of localized ectopic mineralization nodules.

A, Examples of clinical images for localization of nodules to connective tissues likely external to intervertebral disc (i.e., anterior longitudinal ligament) or within the intervertebral disc (i.e., anulus fibrosus); indicated by the yellow dotted circles. **B**, The prevalence of localized nodules in individuals across the continuum of DISH. **C**, Number of motion segments involved with localized nodules of ectopic mineralization stratified across the disease continuum. Red line indicates mean and error bars are 95% confidence intervals. Each dot represents an individual. **D**, Association between the bridge score of the motion segments and localization of mineralized nodules in connective tissues at the first image. **E**, Graph of the change in nodule between images within the same individual, stratified by localization of nodules in connective tissues.

scan) or were no longer present (detected only in first scan) (**Figure 4.5E**). A notable proportion of nodules detected external to the intervertebral disc were detected only in the first scan. In contrast, slightly more nodules within the intervertebral disc were only observed in the last scan. It is possible that localized nodules of ectopic mineralization contribute to the pathophysiology of ectopic bridging in the spine.

4.6 Discussion

In this study, we characterized imaging features along the continuum of DISH in 157 individuals with repeated computed tomography images of the thoracic spine (an average of 2.7 years apart). Between the first and last images, 15% of individuals displayed imaging features that lead to a change in diagnosis. Our analysis revealed that progression to early-phase DISH is largely characterized by involvement of previously unaffected motion segments and the occurrence of localized mineralized nodules in the intervertebral disc. In contrast, progression in the severity of DISH is marked by advancing bridge scores of involved motion segments. These findings underscore that both spatial and temporal changes are critical to progression at different points along the disease spectrum.

To date, few studies have evaluated changes in the imaging features of DISH over time with computed tomography (19, 20, 25-27). Our findings of increased prevalence of complete bridges (from 67.7 to 74.1% [+6.4%] of motion segments) in individuals with DISH in both images is in keeping with previous studies reported increases in complete bridging in individuals with DISH from 45.0 to 55.8% [+10.8%] (20), 54 to 59% [+5%] (19), and 31.3 to 38.0% [+6.7%] (25). The elevated initial prevalence reported in the current study is likely attributed to the design of our study that included 100 individuals per decade of life between 20 and 100+ years, resulting in the analysis of individuals at a more advanced age than previous studies. Regardless, these results inform on the progressive nature of DISH following clinical diagnosis (20, 25). Our analysis further showcased the extent of ectopic bridging by highlighting the involvement of early forms of bridging in non-contiguous regions of the thoracic spine.

Few studies have examined the imaging features associated with progression from early-phase DISH to DISH. The current study characterized the imaging features associated with the transition from early-phase DISH to DISH and reported an increase in the frequency of completing bridging from 20.0 to 43.6% (+23.6%) of motion segments. Kuperus et al. reported increased complete bridging in the group they classified as "pre-DISH" (DISH confirmed on last scan and not on first scan) from 11.3 to 31.0% (+19.7%) of motion segments (20). Thereby, our observations revealed progressive changes from early-phase DISH to DISH occurred over an average of 2.4 years.

By assessing the continuum of DISH, we are the first to explicitly characterize features associated with the onset of early-phase DISH, progression from early-phase DISH to DISH, as well as the progression in severity of DISH. We demonstrated that progression to early-phase DISH is primarily characterized by involvement of new motion segments. Meanwhile, progression in disease severity in individuals with DISH is primarily characterized by advanced bridging. This information is crucial to better understand the clinical features of DISH throughout the disease and suggests that future therapeutic interventions aimed to prevent onset or delay progression may have greater efficacy at different time points in the natural course of the disease.

Our study evaluated both female and male individuals throughout the continuum of DISH (e.g., sample population is 47.1% male and 56.3% of individuals with DISH were male). From this, our results suggest that imaging features associated with progressive change in DISH do not differ based on sex, despite a well-known sex-related difference in the prevalence of the condition (2). The greater prevalence among male individuals may be linked to behaviors and/or societal roles in adulthood that predisposes male individuals to greater spinal trauma and, in turn, the sequalae of DISH. Recently, genetic polymorphisms have been indicated in DISH (28, 29). As such, genetic factors may be a critical feature that differentiates those at risk for advanced pathological mineralization. Since the current population was largely imaged for reasons related to trauma, it would be interesting to explore the association between physical trauma and the potential initiation or accelerated progression of ectopic mineralization associated with DISH.

A strength of the current study was the detailed evaluation of all motion segments in the thoracic spine. We speculate that there may be unique patterns of bridging in specific regions of the spine that can facilitate early disease detection. We recommend modification of scoring systems to differentiate between gross features of complete bridges (e.g., horizontal outgrowths vs. flowing bands) (19-21) and to consider the primary direction of bridge progression. Moreover, we postulate that additional features, such as localized nodules of mineralization documented by us and others (19-21), constitute important pathological features of DISH that should be considered. Previous microcomputed tomography-based characterization of the radiodensity of ectopic mineralization in DISH reported on unique features of hyperdense material and dystrophic calcification (21, 30), likely corresponding to the nodules observed in this study. An increased prevalence of intervertebral disc mineralization with advanced age has been reported in individuals with DISH, along with more complete bridging of the vertebral bodies (27). Interestingly, our investigation of localized nodules showed a significant association with early-phase DISH compared to advanced presentations of DISH and reduced prevalence of localized nodules in the last image. We speculate that localized nodules may be either resorbed with time or become integrated within the forming ectopic bridge associated. It is possible that a relationship between bridge scoring and localized nodules may differentiate pathophysiological stages of DISH.

The current study would be strengthened by increases to both the number of individuals included, as well as the number of scans from each to better capture disease progression. Examination of individuals at distinct time intervals may further distinguish acute and chronic changes associated with the continuum of DISH. Of note, the patient population examined in the current study was not controlled, so other disease(s) may have had influence the progression of pathological mineralization. For example, ossification of other spinal ligaments or peripheral structures may influence the progression of DISH (31, 32). The sample studied was also limited to a group of individuals that are predominately white and reside in a single geographic region in the United States, which hinders the generalizability of our findings to other populations. Lastly, the imaging features described represent only one aspect of the clinical profile and would be strengthened by analysis of the correlation of these to symptoms or impairments.

In conclusion, our detailed analysis of 78 individuals with notable changes in disease features along the continuum of DISH revealed remarkable patterns of pathological changes based on the stage of disease. Early-phase DISH is characterized by the involvement of previously unaffected motion segments and the occurrence of discrete, localized nodules of ectopic mineralization. At early stages, therapies should be aimed at preventing the onset of tissue mineralization. In contrast, increased DISH severity is characterized by the progressive bridging of motion segments previously affected. At later stage, therapies may be effective if they target the processes underlying growth of bridging bony formations. Clearly defining the pathological changes associated with the continuum of DISH will contribute to improved understanding of disease pathogenesis to facilitate targeted clinical management and enhance clinical outcomes.

4.7 References

1. Forestier J, Rotes-Querol J. Senile ankylosing hyperostosis of the spine. Annals of the Rheumatic Diseases. 1950;9(4):321-30.

2. Fournier DE, Leung AE, Battie MC, Seguin CA. Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) and early-phase DISH across the lifespan of an American population. Rheumatology 2023. doi: 10.1093/rheumatology/kead362

3. Utsinger PD. Diffuse idiopathic skeletal hyperostosis. Clinics in Rheumatic Diseases. 1985;11(2):325-51.

4. Al-Herz A, Snip JP, Clark B, et al. Exercise therapy for patients with diffuse idiopathic skeletal hyperostosis. Clinical rheumatology. 2008;27(2):207-10.

5. Katzman WB, Huang MH, Kritz-Silverstein D, et al. Diffuse idiopathic skeletal hyperostosis (DISH) and impaired physical function: The rancho bernardo study. Journal of the American Geriatrics Society. 2017;65(7):1476-81.

6. Harlianto NI, Kuperus JS, Mohamed Hoesein FAA, et al. Diffuse idiopathic skeletal hyperostosis of the cervical spine causing dysphagia and airway obstruction: An updated systematic review. Spine J. 2022;22(9):1490-503.

7. Nathan H. Osteophytes of the spine compressing the sympathetic trunk and splanchnic nerves in the thorax. Spine. 1987;12(6):527-32.

8. Haskard DO, Panayi GS. Multiple peripheral nerve entrapment in forestier's disease (diffuse idiopathic skeletal hyperostosis). Rheumatology. 1988;27(5):407-8.

9. Oh GS, Ju CI, Kim SW, et al. Complete cord injury after minimal trauma in a patient with forestier's disease accompanying ossification of the posterior longitudinal ligament. Journal of Korean Neurosurgical Society. 2007;42(6):487-9.

10. Yamada K, Satoh S, Hashizume H, et al. Diffuse idiopathic skeletal hyperostosis is associated with lumbar spinal stenosis requiring surgery. Journal of Bone and Mineral Metabolism. 2019;37(1):118-24.

11. Tsuji O, Suda K, Takahata M, et al. Early surgical intervention may facilitate recovery of cervical spinal cord injury in DISH. Journal of Orthopaedic Surgery. 2019;27(1).

12. Okada E, Yoshii T, Yamada T, et al. Spinal fractures in patients with diffuse idiopathic skeletal hyperostosis:A nationwide multi-institution survey. Journal of Orthopaedic Science. 2019;24(4):601-6.

13. Okada E, Shimizu K, Kato M, et al. Spinal fractures in patients with diffuse idiopathic skeletal hyperostosis: Clinical characteristics by fracture level. Journal of Orthopaedic Science. 2019;24(3):393-9.

14. Dan Lantsman C, Barkay G, Friedlander A, et al. Whole spine ct scan for the detection of acute spinal fractures in diffuse idiopathic skeletal hyperostosis patients who sustained low-energy trauma. Spine. 2020;45(19):1348-53.

15. Guiot A, Estublier C, Gaude M, et al. Relationship between diffuse idiopathic skeletal hyperostosis and fragility vertebral fracture: A prospective study in older men. Rheumatology (Oxford, England). 2021;60(5):2197-205.

16. Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: Clinical features and pathogenic mechanisms. Nature Reviews Rheumatology. 2013;9(12):741-50.

17. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology. 1976;119(3):559-68.

18. Baraliakos X, Listing J, Buschmann J, et al. A comparison of new bone formation in patients with ankylosing spondylitis and patients with diffuse idiopathic skeletal hyperostosis: A retrospective cohort study over six years. Arthritis and rheumatism. 2012;64(4):1127-33.

19. Yaniv G, Bader S, Lidar M, et al. The natural course of bridging osteophyte formation in diffuse idiopathic skeletal hyperostosis: Retrospective analysis of consecutive ct examinations over 10 years. Rheumatology (United Kingdom). 2014;53(11):1951-7.

20. Kuperus JS, Buckens CF, Šprem J, et al. The natural course of diffuse idiopathic skeletal hyperostosis in the thoracic spine of adult males. Journal of Rheumatology. 2018;45(8):1116-23.

21. Fournier DE, Norley CJD, Pollmann SI, et al. Ectopic spinal calcification associated with diffuse idiopathic skeletal hyperostosis (DISH): A quantitative micro-ct analysis. Journal of Orthopaedic Research. 2019;37(3):717-26.

22. Kuperus JS, Oudkerk SF, Foppen W, et al. Criteria for early-phase diffuse idiopathic skeletal hyperostosis: Development and validation. Radiology. 2019;291(2):420-6.

23. St Sauver JL, Grossardt BR, Yawn BP, et al. Data resource profile: The rochester epidemiology project (rep) medical records-linkage system. Int J Epidemiol. 2012;41(6):1614-24.

24. Rocca WA, Yawn BP, St Sauver JL, et al. History of the rochester epidemiology project: Half a century of medical records linkage in a us population. Mayo Clin Proc. 2012;87(12):1202-13.

25. Murakami Y, Morino T, Hino M, et al. Progression of ossification of the anterior longitudinal ligament associated with diffuse idiopathic skeletal hyperostosis by age: A study of computed tomography findings over 5 years. Global Spine Journal. 2021;11(5):656-47.

26. Murakami Y, Morino T, Hino M, et al. Imaging features of early diffuse idiopathic skeletal hyperostosis (pre-DISH): Analysis of progression of ligament ossification over 5 years by computed tomography. Spine Surgery and Related Research. 2023;Advance Online Publication.

27. Phang SY, Barrett C, Purcell M. A radiological study of the natural history of diffuse idiopathic skeletal hyperostosis (DISH): A story of incomplete fusion. Br J Neurosurg. 2023:1-10.

28. Couto AR, Parreira B, Power DM, et al. Evidence for a genetic contribution to the ossification of spinal ligaments in ossification of posterior longitudinal ligament and diffuse idiopathic skeletal hyperostosis: A narrative review. Frontiers in Genetics. 2022;13.

29. Sethi A, Ruby JG, Veras MA, et al. Genetics implicates overactive osteogenesis in the development of diffuse idiopathic skeletal hyperostosis. Nat Commun. 2023;14(1):2644.

30. Fournier DE, Kiser PK, Beach RJ, et al. Dystrophic calcification and heterotopic ossification in fibrocartilaginous tissues of the spine in diffuse idiopathic skeletal hyperostosis (DISH). Bone Research. 2020;8(1).

31. Kuperus JS, Waalwijk JF, Regan EA, et al. Simultaneous occurrence of ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis: A systematic review. Rheumatology (United Kingdom). 2018;57(12):2120-8.

32. Singh NA, Shetty AP, Jakkepally S, et al. Ossification of posterior longitudinal ligament in cervical spine and its association with ossified lesions in the whole spine: A cross-sectional study of 2500 ct scans. Global Spine Journal. 2023;13(1):122-32.

Chapter 5

Ectopic Mineralization of the Costovertebral Joint and Diffuse Idiopathic Skeletal Hyperostosis (DISH): Micro-CT-based Characterization

Authored by Dale E. Fournier, Alice Zheng, and Cheryle A. Séguin.

5.1 Co-authorship statement

Dale E. Fournier lead study design with contributions from CAS. AZ assisted with CVJ scoring and inter-rater reliability. Dale E. Fournier performed data analysis and illustrations. Manuscript was written by Dale E. Fournier with suggestions from CAS.

5.2 Chapter summary

Mineralized CVJ is linked to respiratory dysfunction. We investigated the association between imaging features of CVJ mineralization and DISH.

Ectopic mineralization of CVJ was analyzed using microcomputed tomography scans of the thoracic spine from 41 human cadavers (mean age 79 ± 9 years). A novel scoring system enabled characterization of joint bridging and intra-articular features of ectopic mineralization.

All specimens displayed some phases of CVJ bridging, features that were detected throughout the thoracic spine. Overt ectopic bridging was 3.0 times more likely in CVJs from specimens with DISH ($p<.001$) and 1.4 times more likely in males ($p=.04$). Ectopic bridging did not display preferential occurrence by side.

Diffuse intra-articular mineral was associated with CVJs from female specimens ($p<0.001$) and the without group ($p<.001$). Distinct intra-articular nodules were 3.3 times more likely in CVJ from specimens with DISH ($p<0.001$).

Regions with complete vertebral bridges meeting the criteria for DISH were 4.5 and 2.7 times more likely to display overt ectopic bridging and intra-articular distinct nodules >.430 mm3 compared to regions without vertebral bridging, respectively. Only ectopic CVJ bridging (39.1% of CVJs) was more common than co-localized ectopic bridging and intra-articular mineral (25.5%), or only intra-articular mineralization (13.4%).

Imaging features of ectopic mineralization of the CVJ are common throughout the continuum of DISH. CVJ involvement may contribute to clinical symptoms of respiratory impairment in DISH and may be a valuable addition to its diagnostic criteria using computed tomography scans. Intra-articular involvement of the CVJ may also contribute to the pathogenesis of DISH.

5.3 Introduction

The CVJ is the articulation between the head of the rib and vertebrae (1). These synovial joints are surrounded by connective tissues that are richly innervated and susceptible to pathology (2-5). Previous studies showed CVJ changes in osteoarthritis and rheumatoid arthritis of the spine (6-8), as well as seronegative spondyloarthropathies (9-11). Joint space narrowing, bone erosions, joint ankylosis, or osteophyte bridging are pathological features that can impair rib mobility and result in respiratory dysfunction and/or pain (12-16). Mineralized outgrowths can disrupt neurovascular structures and create additional symptoms (1, 17-19).

CVJ involvement is generally overlooked due to the challenges of viewing imaging features with plain film radiographs (20). Advanced medical imaging improves investigation of disease features associated with CVJs and facilitates insight into the clinical relevance with musculoskeletal conditions (21, 22). One such musculoskeletal condition that may involve CVJ changes is DISH, a noninflammatory enthesopathy characterized by the formation of ectopic mineral bridges along the vertebral bodies of the spine (23) that affects one in four individuals over 60 years of age (24). Since DISH is associated with ectopic mineral formation (25), it reasons that CVJs could likewise undergo pathological mineralization and contribute to symptoms of DISH. Previous studies showed the occurrence of pathological bridging of the CVJ in DISH (26-28) and linked with impaired respiratory function (29, 30).

The purpose of this study was to characterize the imaging features of CVJs across the continuum of DISH in a sample of human cadaveric spines using micro-CT. We investigated the association between ectopic mineralization of the CVJ and DISH by employing a novel semi-quantitative scoring system to assess the extent and localization of ectopic mineral formation.

5.4 Methods

This study included thoracic spines from a previously characterized cohort of 59 embalmed human cadavers (27 females, 32 males; mean age at death = 79 years, 55 to 96) from the Haase Education in Anatomy & Research Technologies Laboratory at the University of Western Ontario. All data were obtained in accordance with the Anatomy Act of Ontario and the study was approved by Western's Committee for Cadaveric Use in Research (#22062016, **Appendix E**). Cadaver donors were white from Southwestern Ontario. Sex as a dimension was defined by biological attributes associated with physical features. No personal or medical information was available. Thoracic spines were dissected and imaged using micro-CT (31).

5.4.1 Classification of DISH and features of ectopic spine mineralization

A blinded clinician-evaluator assessed the micro-CT scans to determine DISH status based on Resnick and Niwayama's radiographic criteria (32): i) ectopic mineral bridges across four contiguous vertebrae, ii) normal to mildly decreased intervertebral disc height, and iii) lack of erosions, sclerosis, or bony fusion of the zygapophyseal or sacroiliac joints. The sacroiliac joints were not dissected and thus could not be evaluated. Early-phase DISH was determined by the presence of fewer than three contiguous bridged motion segments with adjacent incomplete bridges in the thoracic spine, based on recently reported criteria (33). Three groups were established: specimens meeting the diagnostic criteria for DISH, early-phase DISH, or not meeting either criterion. Stratified sampling using randomly assigned identifiers ensured representation of sex and the continuum of DISH. Specimens with imaging features of ankylosing spondylitis or significant damage from post-mortem dissection were excluded. A semi-quantitative scoring system was used to evaluate the completeness of vertebral bridging at each motion segment (34).

5.4.2 Assessment of the CVJ

A scoring system to evaluate ectopic CVJ mineralization was created based on features similar to ectopic bridging in the spine (35) (**Figure 5.1**). We focused on the presence and extent of CVJ bridging between the head of the rib and the vertebrae, as well as the presence and appearance of mineralized material within the joint space. Multiple training sessions were conducted and independent evaluations for inter-rater reliability analysis were performed using all CVJs from three randomly selected specimens.

All images were de-identified for scoring and image order was randomized. Multiplanar micro-CT reconstructions were cropped to contain a single motion segment with the associated ribs. Images were viewed using MicroView (2.5.0: Parallax Innovations Inc., Ilderton, ON) at a consistent window and level (3000, 500). The transverse plane was

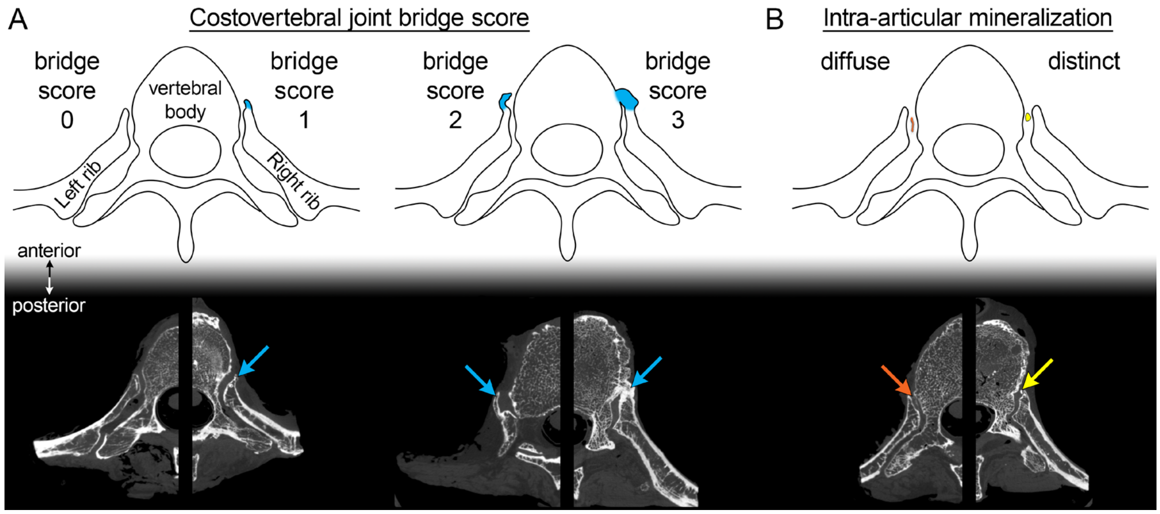

Figure 5.1. Schematic depiction of the novel scoring system to evaluate ectopic mineralization of the CVJ

Cranial to caudal view. Representative microcomputed tomography sections are displayed below line drawing. **A**, Costovertebral joint bridge score characterizes the presence of mineral formations bridging the head of the rib and vertebrae (cyan blue color and arrows): 0 = no evidence of ectopic bridging; 1 = minor outgrowth extension; 2 = major outgrowth forming a near-complete bridge; 3 = complete bridge between the head of the rib and vertebrae. **B**, Intra-articular involvement characterizes mineralized material within the joint space. Diffuse material presented as amorphous radiodense material throughout the costovertebral joint (orange colour and arrow). Distinct nodules were classified based on localized material with a definitive border (yellow colour and arrow). Images not drawn to scale.

predominately used to score features of the CVJ. Single motion segments from specimens were excluded when post-mortem dissection compromised the CVJ; this occurred in 24 unique CVJs from 14 individuals. In these instances, the contralateral CVJ from the same rib level was also excluded.

Given the sensitivity of micro-CT to detect small features of mineralization, a second observer evaluated all CVJs with intra-articular mineralization for quantitative analysis. Manual segmentation and computational thresholding were used to quantify the volume of mineralized material using a threshold corresponding to the density of cortical bone (≥400 Hounsfield units) (31). A threshold volume of greater than 0.430 mm3 (50th percentile of data) was set to ensure relevance in the context of clinical imaging protocols.

5.4.3 Statistical analyses

SPSS Statistics (v29.0, IBM Corp., Armonk, NY) was used for data analysis and GraphPad Prism (v8.0, GraphPad Software, San Diego, CA) to create graphs. Data were evaluated for normality using histograms and Shapiro-Wilk test. Reliability was assessed using Cohen's kappa test statistic for paired observations of categorical variables that were scored by the same two independent raters. Dichotomous and dummy coded nominal variables were evaluated for association using chi-square test statistics because observations were independent and exclusive categorical variables. Binomial logistic regression was used to predict the probability of dichotomous CVJ involvement based on exclusive independent variables (disease categorization, sex, sidedness, spine disease activity). Volumetric data of intra-articular mineralization was not normally distributed and required non-parametric tests to compare the medians. Kruskal-Wallis H test was used to compare across disease categories and Mann-Whitney U test to compare between sexes. These non-parametric tests were also used to evaluate ordinal bridge score data by disease category and sex. McNemar test was used to evaluate differences in paired, mutually exclusive categorical data within the same individual.

5.5 Results

5.5.1 Sample characteristics

Scans of 48 specimens were evaluated; three were excluded due to features of inflammatory arthritis in all apophyseal joints and four were excluded due to damage to over half of CVJs associated with post-mortem dissection. The sample included 41 thoracic spine specimens from 19 female and 22 male individuals. The mean age at death was 80 ± 9 years (range 64 to 94). Within the sample, 14 met the diagnostic criteria for DISH (6 female, 8 male individuals), 12 met the criteria for early-phase DISH (5 female, 7 male individuals), and 15 did not meet either criterion (8 female, 7 male individuals). In total, 878 CVJs were evaluated from 439 motion segments in the thoracic spine, corresponding to an average of 73 ± 9 CVJs evaluated at each rib level. Analysis of age did not display any main effects between disease groups ($p=.73$) or sex ($p=.67$), nor interaction effects ($p=.18$).

5.5.2 Inter-rater reliability

Substantial agreement was reported between raters in the sample of 72 CVJs that were evaluated for ectopic bridging and intra-articular mineralization (33). Within the sample of three micro-CT scans of the thoracic spine and, unknown to the raters at the time of evaluation, 63% of CVJs displayed some phase of ectopic bridging and 61% of CVJs displayed intra-articular mineralization.

We focused on ensuring reliable evaluation of bridge score prior to data collection. Within the 72 CVJs evaluated, the raters consistently identified the dichotomous presence of any phase of ectopic bridging (κ=0.82: 95% CI=0.68, 0.96). At least 4% of CVJs displayed complete bridges (score 3), 33% of CVJs displayed near-complete bridges (score 2), and 25% of CVJ displayed some anterior bridging (score 1). Given the ordinal scale of bridging severity, a weighted kappa statistic was reported (κ=0.79; 95% CI=0.68, 0.89).

We also evaluated inter-rater reliably to detect intra-articular mineralization of the CVJ. Unknown to the raters at the time of evaluation, at least 50% of CVJs displayed intra-articular mineralization. The raters consistently identified the dichotomous presence of any type of intra-articular mineralization (κ=0.77; 95% CI=0.63, 0.92). Within regions identified with intra-articular mineralization, 18% displayed the diffuse presentation and 82% the distinct presentation, for which perfect agreement in its classification was achieved (κ=1.0). After which, AZ independently evaluated all scans of the CVJ and DEF reviewed all CVJs identified with intra-articular mineral.

5.5.3 Ectopic bridging of the CVJ

Ectopic bridging between the head of the rib and vertebra was scored based on the extent of connection between the two structures (**Figure 5.1A**). Any phase of bridging (score 1, 2, or 3) were observed in at least one CVJ in each specimen and 64.6% of total CVJs assessed, averaging 14 ± 5 CVJs per specimen (range 4 to 22). Ectopic bridges mostly extended from the rib towards the vertebra (70.2% of CVJs with bridges). Complete ectopic bridges linking the rib and vertebra (score of 3) were uncommon, likely due to the resolution enabled by micro-CT; detected in 1.9% of all CVJs.

Associations were found between the prevalence of CVJ bridging and disease category as well as sex (**Figure 5.2A**). The occurrence of any phase of CVJ bridging was more common in specimens with DISH ($p<0.001$), slightly more frequent in specimens with early-phase DISH ($p=.36$), and less common in the without group ($p<0.001$) (**Figure 5.2B**). Complete ectopic bridges were most often observed in specimens with DISH (76.5%), and almost exclusively among males (92.3%). Over 50% of CVJs from specimens in the without group displayed evidence of ectopic bridging. Irrespective of disease category, an association was demonstrated between any phase of CVJ bridging and male sex (68% of CVJs compared to 61% in females; $p=.03$). The probability of CVJ bridging was 1.2 times greater (95% CI=.92, 1.6) in male compared to female specimens ($p=.13$).

A logistic regression analysis was performed to ascertain the effects of disease category and sex on CVJ bridging. The likelihood of detecting features of ectopic CVJ bridging was 3.0 times greater for specimens with DISH (95% CI=2.1, 4.3; $p<0.001$) and 1.8 times greater for specimens with early-phase DISH (95% CI=1.3, 2.5; $p<0.001$) compared to the without group. Overall, there was an increase in CVJ bridging in both sexes with increased disease severity (**Figure 5.2B**). The most notable sex-related difference was an increased percentage of complete ectopic bridges in male compared to female individuals in specimens with DISH (7.1% compared to 1.8%; $p=.05$).

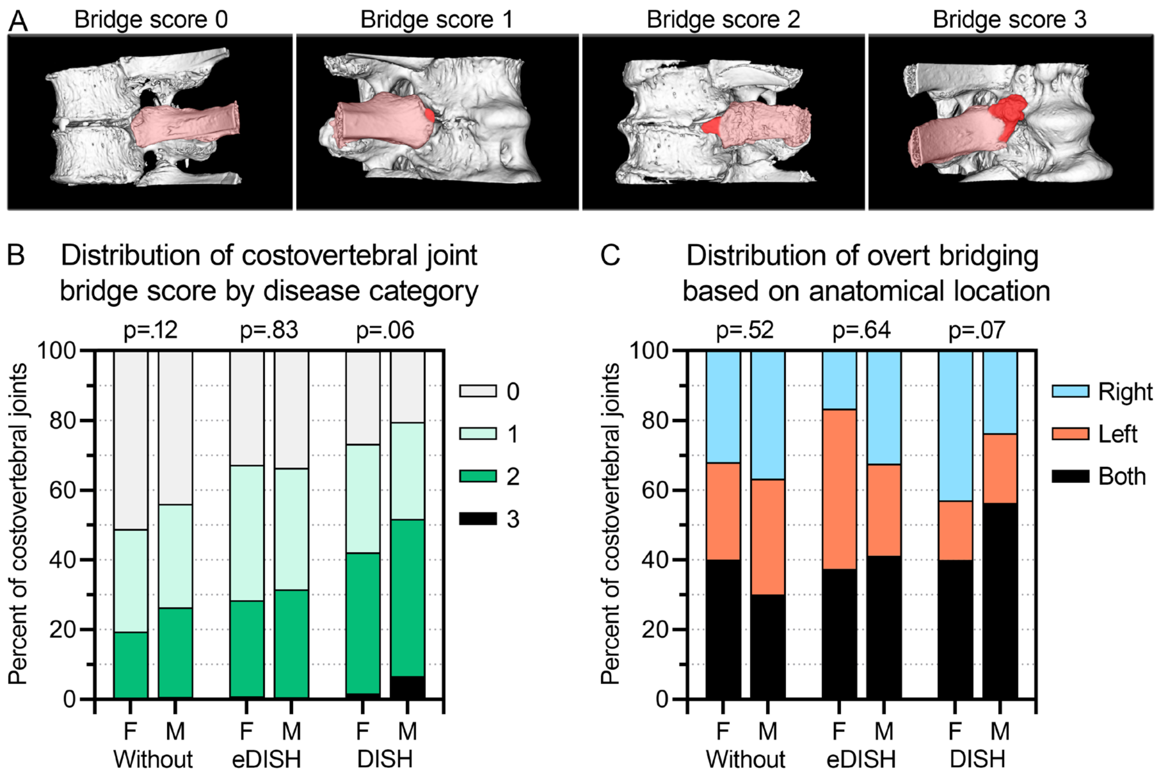

Figure 5.2. Analysis of CVJ bridging across the continuum of DISH, stratified by sex

A, Representative three-dimensional renderings of the continuum of bridge scores. Pseudo-coloured in light red is the rib of interest and darker red highlights areas of ectopic bridging. **B**, Graph displays the distribution of bridge scores in each group, presented as percent of all costovertebral joints evaluated. **C**, Graph displays the distribution of overt bridging (scores 2 and 3) based on costovertebral joint sidedness. Data are presented as the percentage of costovertebral joints displaying the associated imaging features. P values indicate comparison between sexes for each disease category using Mann-Whitney U test. F, female; M, male; eDISH, early-phase DISH.

To focus on bridging features that would be readily detected with clinical imaging protocols, we assessed the prevalence of overt CVJ bridging (scores 2 and 3). Overt CVJ bridging was more common in specimens with DISH and less common in the without group ($p<0.001$). No association was observed between overt bridging and specimens with early-phase DISH ($p=.24$). Increased overt CVJ bridging was detected in male compared to female specimens ($p=.01$; stratified by bridge score of 2, $p=.03$; and bridge score of 3, $p=.05$). Logistic regression confirmed greater odds of overt CVJ bridging in specimens with DISH (OR=3.0; 95% CI=2.1, 4.3; $p<0.001$) and in male individuals (OR=1.4; 95% CI=1.0, 1.8; $p=.04$). Conversely, an association between early ectopic bridging (score of 1) and early-phase DISH was noted ($p=.03$).

Given the right-sided predominance of ectopic spine bridging in DISH (31, 35), we investigated the relationship between sidedness and CVJ bridging (**Figure 5.2C**). Overall, paired comparison tests indicated that sidedness within a motion segment did not affect the prevalence of CVJ bridging ($p=.79$), overt bridging ($p=.46$), or the distribution of bridge scores ($p=.40$).

We next assessed the anatomical localization of CVJ bridging. Ectopic bridging was observed in all regions of the thoracic spine in specimens from all disease categories (**Figure 5.3**). Across both sides of the entire cohort, any phase of CVJ bridging was statistically less common in the first two ribs compared to the other regions of the thoracic spine. CVJ bridging was associated with rib six ($p=.01$), seven ($p=.01$), and eight ($p=.04$); and overt CVJ bridging was also associated with rib seven ($p<0.001$), eight ($p<0.001$), as well as nine ($p=.002$).

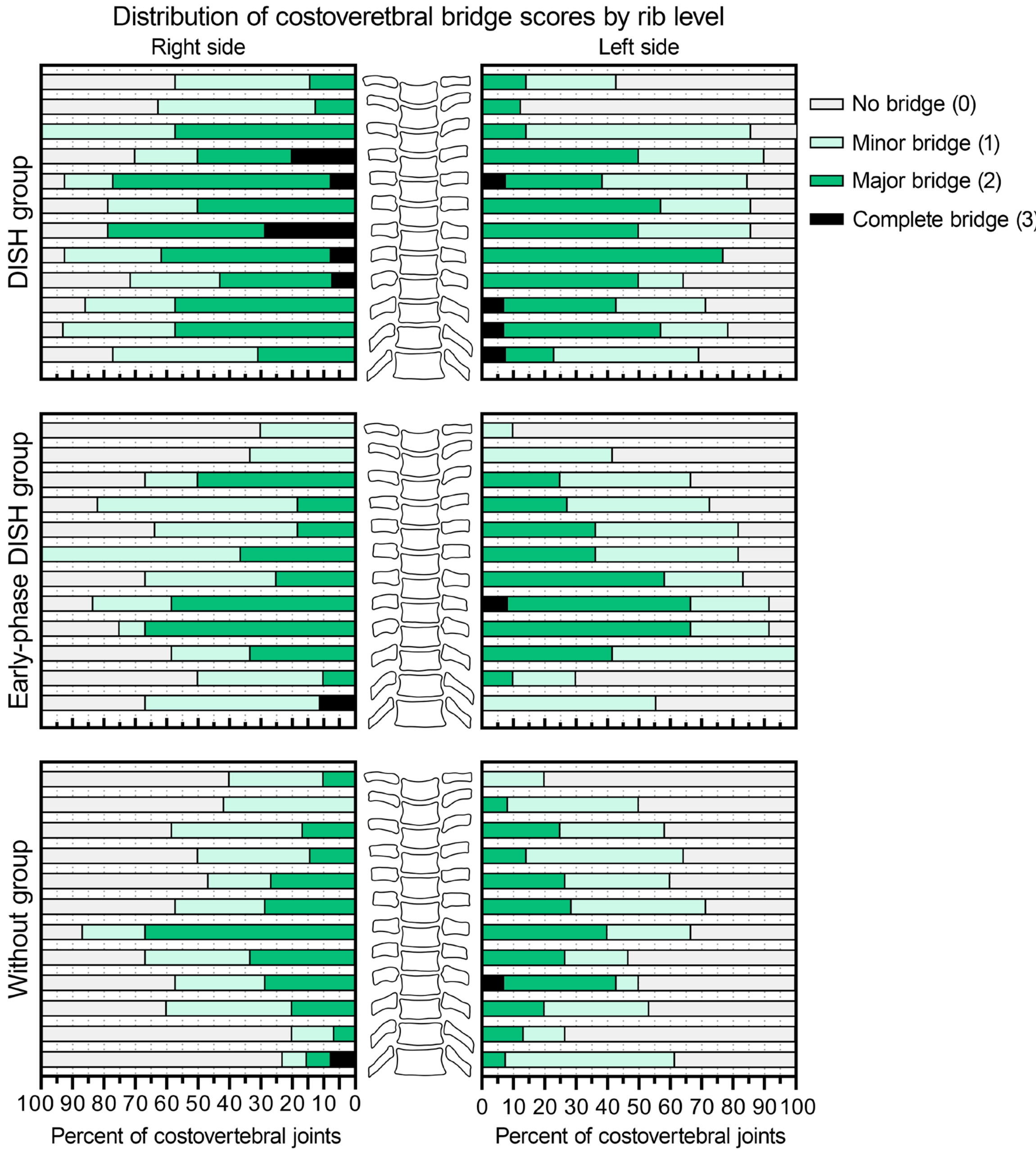

Figure 5.3. Visualization of the prevalence and severity of CVJ bridging stratified by disease category and side

Data from ribs one through twelve are displayed for each disease category. Data are presented as the percentage of costovertebral joints displaying the associated imaging features.

To contextualize the heterogeneity in CVJ bridging observed, we investigated the relationship with spine bridging as a reflection of DISH disease severity across the specimens (**Table 5.1**). Motion segments without spine bridging comprised the reference group for logistic regression. The extent of spine bridging was scored using a classification system by Yaniv and colleagues.(34) Complete spine bridges were stratified as being localized to regions meeting the diagnostic criteria for DISH (i.e., minimum of three consecutive ectopic bridges connecting four vertebral bodies) or other involved regions of the thoracic spine.

5.5.4 Intra-articular CVJ mineralization

Ectopic mineralization within the joint space was identified in 39.2% of all CVJs corresponding to 40 of 41 specimens. Intra-articular mineralization was detected, on average, in eight CVJs (range 0 to 22) per individual. Two distinct types of intra-articular mineralization were noted: i) diffuse material throughout the CVJ space; and ii) radiodense nodules with distinct borders (**Figure 5.1B**).

Diffuse intra-articular material was detected in 19.9% of CVJs. Diffuse mineralization was significantly more common in female specimens ($p<0.001$) and those in the without group ($p<0.001$) (**Figure 5.4A**). Diffuse intra-articular material was slightly more common in male specimens with DISH compared to females ($p=.07$). In contrast, diffuse material was strongly associated with female specimens with early-phase DISH compared to males ($p<0.001$).

Logistic regression analysis was performed to determine the effects of disease category and sex on the probability of detecting diffuse intra-articular mineral in the CVJ. Sex was

Table 5.1. Logistic regression analysis of extra-articular bridging and disease activity

	Extra-articular bridging of the CVJ					
Vertebral disease activity	Minor bridging			Overt bridging		
	OR	95% CI	p value	OR	95% CI	p value
No bridge	1			1		
Incomplete bridge	4.2	1.3, 14.1	.020	1.6	.62, 3.9	.343
Complete bridge: outside of DISH region	5.5	1.5, 20.3	.011	1.8	.62, 5.1	.282
Complete bridge: within DISH region	3.2	.91, 11.0	.071	4.5	1.7, 11.6	.002

Notes: Vertebral disease activity definitions: No bridge, vertebral bridge score of 0; Incomplete bridge, vertebral bridge score of 1-5 using Yaniv scoring system; Complete bridging, outside of DISH region, vertebral bridge score of 6 using Yaniv scoring; Complete bridging, within of DISH region, vertebral bridge score of 6 using Yaniv scoring system that met the diagnostic criteria for DISH (i.e., three contiguous complete bridges). OR, odds ratio; CI, confidence interval; DISH, diffuse idiopathic skeletal hyperostosis.

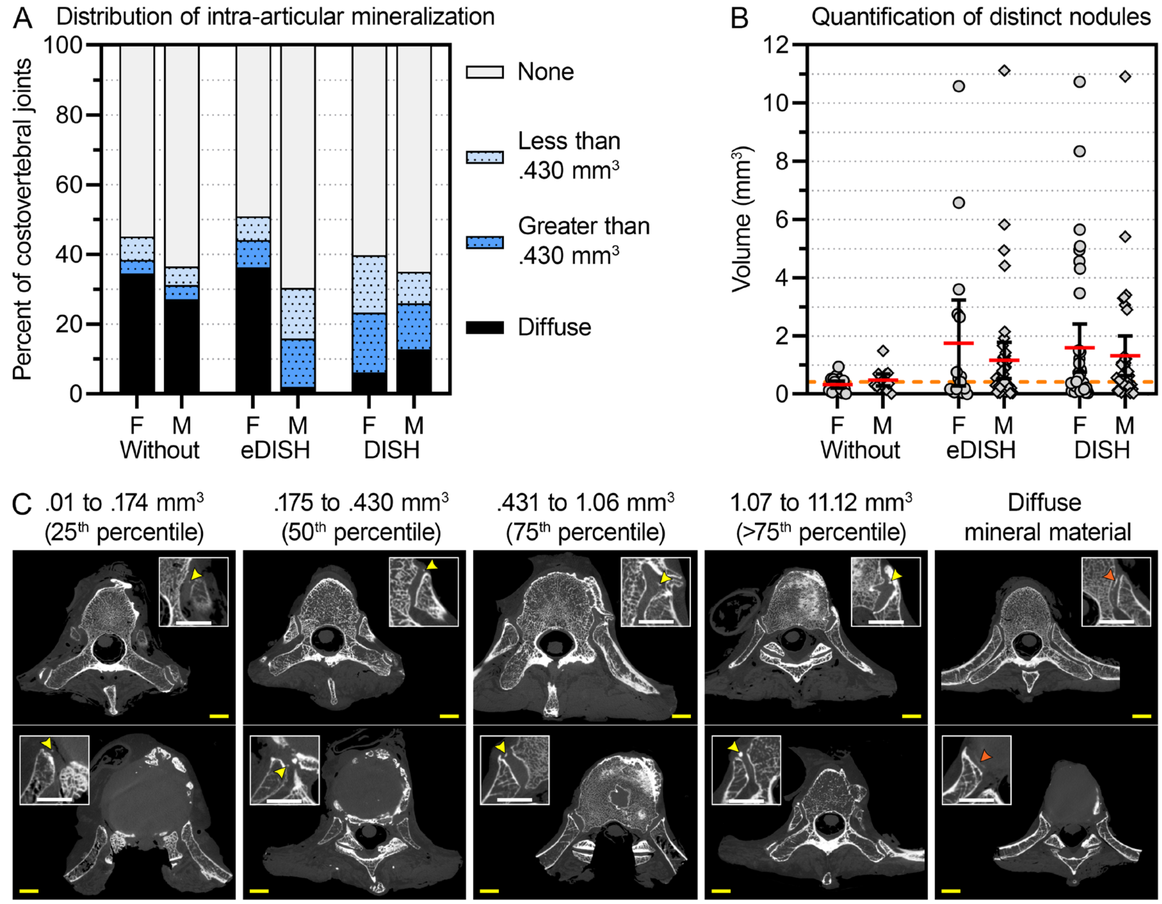

Figure 5.4. Analysis of intra-articular mineralization of the CVJ

A, Graph displays the prevalence of intra-articular mineralization across the disease continuum and stratified by sex. Data are presented as the percentage of costovertebral joints displaying the associated imaging features. **B**, Graph displays the volume of focal mineralized material within costovertebral joints identified as distinct nodules. Orange dotted line indicates inclusion threshold (50th percentile of data). Data are summarized as means with 95% confidence intervals. F, female; M, male; eDISH, early-phase DISH. **C**, Panels showing images of the different sized nodules observed from the 25th percentile to greater than the 75th percentile. Two unique presentations of the diffuse presentation are shown. Scale bars represent 10 mm. Arrowheads highlight the intra-articular mineralization in each image.

found to be a significant factor with female specimens 2.1 times more likely (95% CI=1.5, 3.0; $p<0.001$) to show diffuse intra-articular CVJ material compared to male specimens. In contrast, CVJ from specimens with DISH and early-phase DISH were 74% (95% CI=.26, .42; $p<0.001$) and 52% (95% CI=.32, .72; $p<0.001$) less likely to display diffuse intra-articular material, respectively, compared to specimens in the without group.

Micro-CT enabled quantification of the volume of distinct nodules through segmentation and computational thresholding. Distinct mineralized nodules of various sizes were observed in the intra-articular space in 19.2% of CVJs (**Figure 5.4B and 5.4C**). Distinct nodules of any size were significantly associated with DISH ($p<0.001$), slightly more common in early-phase DISH ($p=0.12$), and were less frequent in the without group ($p<0.001$). No sex-related differences were noted ($p=.46$). When stratified by disease category, distinct nodules were more common in CVJs from female specimens with DISH ($p=.04$) and male specimens with early-phase DISH ($p=.008$). Logistic regression analysis predicts that CVJs from specimens with DISH are 3.3 times (95% CI=2.1, 5.2; $p<0.001$) more likely to have distinct nodules compared to the without group. Meanwhile, specimens assigned to early-phase DISH were 2.6 times (95% CI=1.6, 4.1; $p<0.001$) more likely to present with CVJ nodules than the without group. Sex was not a significant predictor of the involvement of distinct nodule ($p=.95$).

The volume of distinct nodules ranged from .007 to 11.1 mm3 and there was no statistical difference between sex or sidedness. The average volume was greater in specimens with DISH compared to the without group ($p=.08$) and no differences were detected between DISH and early-phase DISH. After applying the threshold to focus our analysis on nodules that could be detected with clinical imaging protocols (>0.430 mm3), the prevalence of distinct nodules was reduced to 9.7% of CVJs. Larger nodules remained strongly associated with DISH ($p<0.001$) and DISH disease status remained a significant predictor compared to the without group based on logistic regression analysis (OR=4.1; 95% CI=2.1, 7.8; $p<0.001$). Large distinct nodules were also 3.0 times more likely in specimens with early-phase DISH compared to the without group (95% CI=1.5, 5.9; p=0.001). Sex was not a significant predictor of large distinct nodules.

The relationship between intra-articular nodules, anatomical region, and sidedness was assessed (**Figure 5.2**). All rib levels displayed evidence of intra-articular CVJ mineral formation, with no statistical differences detected in the overall prevalence of intra-articular involvement, prevalence of all threshold intra-articular mineral, or the disease groups based on sidedness. Diffuse mineralization was observed throughout the thoracic spine, except for the twelfth rib that was less involved (p=.03). Distinct nodules of all sizes were associated with increased prevalence in the mid-thoracic spine; rib six (p=.13) and seven (p=.02). Large distinct nodules were observed slightly less at ribs three (p=.08) and five (.07), and slightly more at rib twelve (p=.07). Analogous to ectopic bridging of CVJs, we examined the relationship between intra-articular CVJ mineralization and ectopic spine bridging as a reflection of DISH disease severity (**Table 5.2**).

Lastly, we assessed the relationship between CVJ bridging and intra-articular mineralization (either diffuse or distinct nodules) within the same joint. CVJ bridging

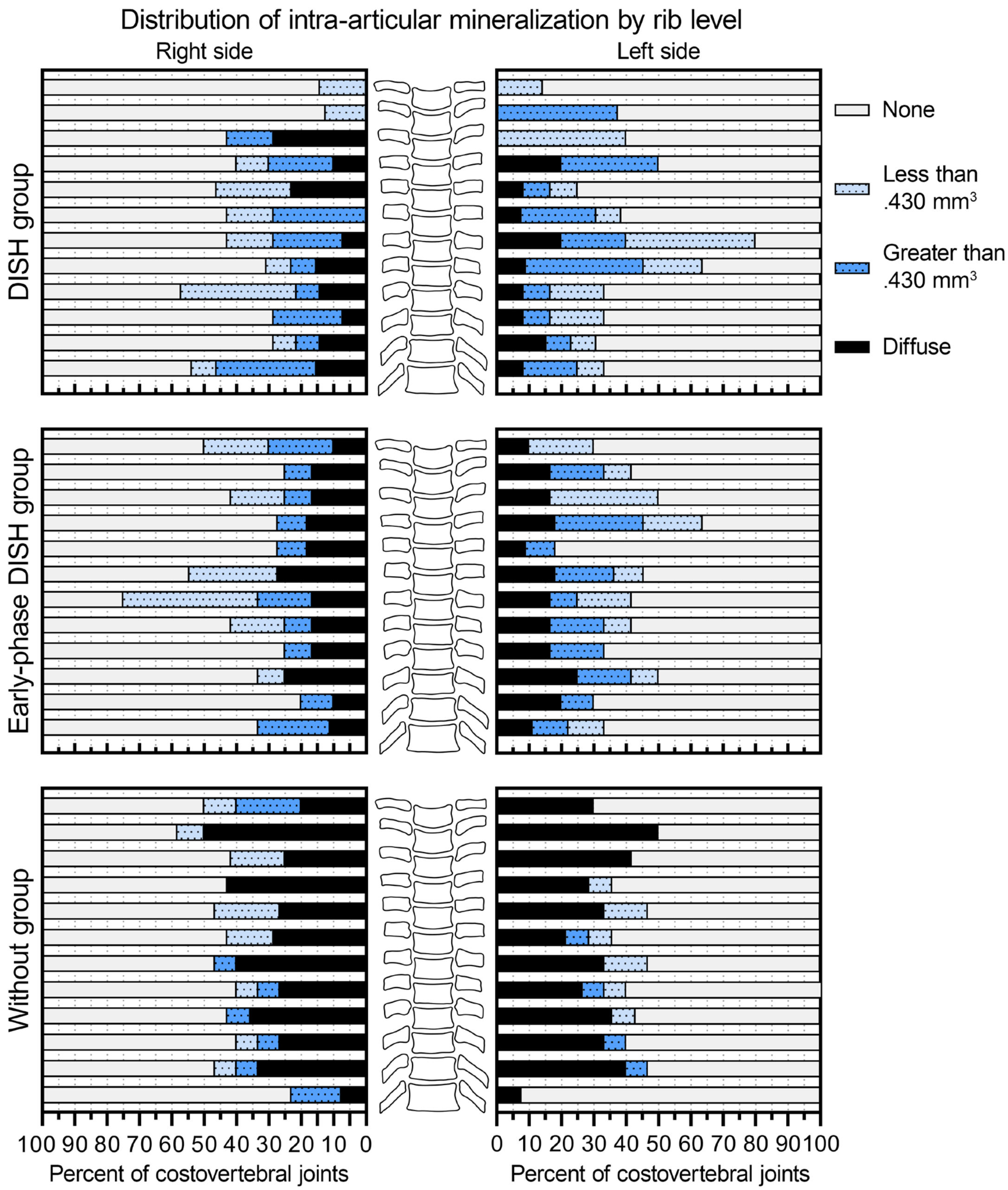

Figure 5.5. Visualization of the prevalence and type of intra-articular CVJ mineralization stratified by disease category and side

Data from ribs one through twelve are displayed for each disease category. Data are presented as the percentage of costovertebral joints displaying the associated imaging features.

Table 5.2. Logistic regression analysis of intra-articular involvement and disease activity

Vertebral disease activity	Intra-articular mineralization in the CVJ								
	Diffuse mineral			Distinct nodules (all sized)			Distinct nodules (large only)		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
No bridge	1			1			1		
Incomplete bridge	2.8	.85, 9.6	.090	1.1	.38, 3.3	.830	.97	.22, 4.2	.970
Complete bridge: outside of DISH region	1.1	.27, 4.8	.854	1.9	.57, 6.5	.298	2.7	.55, 13.3	.220
Complete bridge: within DISH region	.60	.16, 2.3	.455	2.6	.84, 7.8	.097	2.7	.60, 11.9	.197

Notes: Vertebral disease activity definitions: No bridge, vertebral bridge score of 0; Incomplete bridge, vertebral bridge score of 1-5 using Yaniv scoring system; Complete bridging, outside of DISH region, vertebral bridge score of 6 using Yaniv scoring; Complete bridging, within of DISH region, vertebral bridge score of 6 using Yaniv scoring system that met the diagnostic criteria for DISH (i.e., three contiguous complete bridges). OR, odds ratio; CI, confidence interval; DISH, diffuse idiopathic skeletal hyperostosis.

and intra-articular mineralization co-localized in 25.5% of CVJs assessed (**Figure 5.6**). Overall, it was more common to observe only bridging (39.1% of CVJs) than only intra-articular mineralization (13.7% of CVJs). The most notable sex-related differences were the increased co-localization of CVJ bridging and intra-articular mineralization of CVJs from female specimens with early-phase DISH (p=.01) and only CVJ bridging in male specimens with early-phase DISH (p=.02). Logistic regression predicts that specimens with DISH are 74% less likely (95% CI=.15, .45; p<0.001) and 69% more likely (95% CI=1.2, 2.5; p=.002) to present with intra-articular only or bridging only, respectively. Co-localization of CVJ bridging and intra-articular mineralization is nearly twice more common in CVJs from specimens with DISH (OR= 1.9; 95% CI=1.3, 2.8; p<0.001) and 65% more likely in CVJs from specimens with early-phase DISH (OR= 1.6; 95% CI=1.1, 2.4; p=.01) compared to the without group. We also explored the relationship between ectopic spine bridging and patterns of ectopic mineralization of the CVJ (**Table 5.3**).

5.6 Discussion

In this study, we characterized features of ectopic mineral formation specific to the CVJ in 41 human cadaver thoracic spine specimens using micro-CT. Although features of CVJ bridging and intra-articular mineralization were detected across the cohort of specimens examined, our detailed characterization demonstrated important associations with DISH. Specifically, we showed that: i) ectopic CVJ bridging was associated with specimens with DISH, particularly males; ii) diffuse intra-articular material in the CVJ was more common in female specimens and the without group; and iii) distinct intra-articular nodules in the CVJ were associated with DISH. Regression analysis predicted greater odds of CVJ bridging and concurrent bridging and intra-articular mineralization

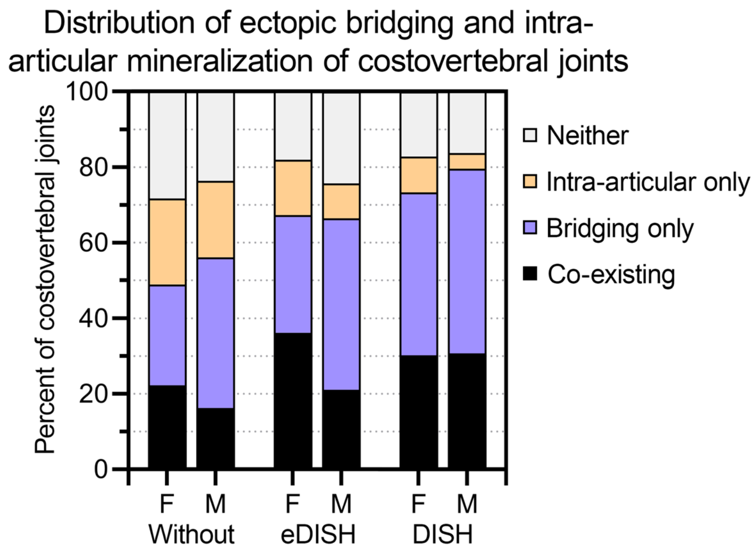

Figure 5.6. Co-localization of CVJ bridging and intra-articular mineralization

Data are shown as the percent of costovertebral joints that displayed imaging features of only costovertebral joint bridging or intra-articular mineralization, or both within the same joint. Data are stratified for analysis by disease categories and sex.

Table 5.3. Logistic regression analysis of co-localization and disease activity

Vertebral disease activity	Relationship of CVJ involvement: Intra-articular only			Bridge only			Both		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
No bridge	1			1			1		
Incomplete bridge	1.5	.42, 5.2	.485	2.8	1.0, 7.4	.041	2.1	.70, 6.1	.183
Complete bridge: outside of DISH region	.96	.22, 4.1	.958	4.0	1.4, 12.0	.013	2.1	.62, 7.0	.232
Complete bridge: within DISH region	.43	.11, 1.7	.231	4.7	1.7, 13.0	.003	2.8	.92, 8.4	.070

Notes: Vertebral disease activity definitions: No bridge, vertebral bridge score of 0; Incomplete bridge, vertebral bridge score of 1-5 using Yaniv scoring system; Complete bridging, outside of DISH region, vertebral bridge score of 6 using Yaniv scoring; Complete bridging, within of DISH region, vertebral bridge score of 6 using Yaniv scoring system that met the diagnostic criteria for DISH (i.e., three contiguous complete bridges). OR, odds ratio; CI, confidence interval; DISH, diffuse idiopathic skeletal hyperostosis.

in regions with ectopic spine bridging meeting the diagnostic criteria for DISH. In contrast to the right-sided predominance of ectopic spine bridging in DISH, sidedness was not a crucial factor for ectopic mineralization of CVJs. These findings highlight the value of examining the CVJs as a key factor contributing to the pathogenesis of DISH.

Previous studies have reported pathological CVJ changes with DISH. Complete fusion and osseous outgrowth of at least one CVJ per individual was reported in 45.7% of those with DISH compared to 6.3% of those without DISH using CT (27). In our study, all specimens with DISH displayed CVJ bridging affecting on average 16 ± 4 individual CVJs. These findings are higher than a previous characterization of a sample of people with DISH and cervical spine injuries that reported CVJ bone excrescence in nearly all individuals (94%, 47 of 50 patients) and affecting an average of 7.0 ± 5.4 joints per individual (37). Previous studies indicate that within the same individual, 26.1% and 15.4% presented with multiple levels of CVJ involvement (22, 38). Our results showed multilevel involvement in 13/14 specimens with DISH (average of 6 levels), 14/16 specimens with early-phase DISH (average of 5 levels), and 8/11 specimens in the without group (average of 4 levels). Of note, in our study complete bridges were identified in 1.9% of all CVJs using micro-CT. A previous study using plain-film radiographs reported complete bridging in 32 of 909 articulations (3.5%) (38). Given the extreme differences in resolution based on imaging modality, we speculate that the prevalence of overt bridges (scores of 2 and 3: 47.9% of CVJs, on average 10 ± 5 per individual) may best reflect what can be observed using clinical imaging.

In terms of anatomical localization, our results align with previous studies that described more ectopic mineralization in the ribs from the mid-thoracic spine and less involvement of the upper ribs (22, 28, 37, 38). We speculate that this pattern may be linked to differences in joint biomechanics across the thoracic spine given that the prevalence of ectopic bridging of the vertebral bodies displays a similar pattern (31). Previous studies suggested greater prevalence of CVJ involvement in DISH on the right compared to the left side (22, 28, 37, 39). In contrast, we did not observe a statistical difference based on sidedness, findings which do align with another previous study (38). While it is theorized that the presence and pulsation of the aorta may drive the predominant right anterolateral involvement of vertebral body bridging in DISH, our findings suggest that this factor may not affect CVJ mineral formation.

DISH as a clinical entity is regularly underreported (Chapter 3) and there is a poor understanding of its clinical implications. Our findings of CVJ bridging suggest that the stiffness resulting from bridging of the spine in DISH may likewise occur at the CVJ, leading to hypomobility in these regions. A clinical study showed that individuals with DISH have lower CT-measured lung volumes and reduced functional respiratory measures compared to individuals without DISH (29, 30). Notably, individuals with DISH had a reduction in the 6-minute walk test without differences in SGRQ scores (measure of impact on daily function), from which the authors concluded that respiratory changes may only be noticed during exercise activities (30). Based on the prevalence of CVJ changes observed in the current study, it reasons that spirometry could be a valuable non-invasive clinical tool used to screen for CVJ impairments related to DISH and/or monitor disease progression. The impact of respiratory dysfunction in DISH also contributes to prognosis for surgical intervention (37). Pre-operative respiratory complications were reported in 40% of people with cervical spine injuries and DISH, and extensive CVJ mineralization was noted in individuals that did not survive five years post-surgery (37). Decreased thoracic mobility increases the risk for complications associated with pneumonia and other respiratory illnesses. It is possible that breathing exercise programs, which have been effective in studies in populations with ankylosing spondylitis, could improve functions of daily life for people with DISH (40-42).

Our results support that clinical features of DISH expand beyond the diagnostic criteria focused on bridging of the vertebral bodies. One value of exploring other joints affected by DISH is the potential influence on its clinical management and better definition of its clinical presentation. For example, inclusion of respiratory symptoms associated with CVJ bridging in the clinical description of DISH may enable clinicians to avoid extraneous testing for symptoms that may seem unrelated to spine mineralization. Additional structures that undergo pathological mineralization may also contribute to respiratory dysfunction or symptoms of pain, including the sternocostal, clavicular, and costotransverse joints, in which ectopic mineralization has been described in previous studies (43-45). Our study provides a novel scoring system to evaluate CVJ mineralization that likely can be adapted to evaluate the involvement of these structures in relation to DISH. The prevalence of CVJ mineralization and the association of specific imaging features with DISH disease stage warrants further study of the clinical relevance of these tissues and their potential inclusion in a modified diagnostic criteria for DISH when using CT.

This study is the first to characterize intra-articular CVJ mineralization in DISH using micro-CT. The nodules detected bear remarkable resemblance to localized nodules we previously described in spinal ligaments and the intervertebral disc with DISH (46). It is unclear whether the intra-articular nodules are a unique feature of DISH or also occur in other pathologies. Within the CVJ, we speculate that diffuse intra-articular mineralization may be a precursor to bridging of the joint given their increased prevalence in tissues from specimens assigned to the without group. The resolution of micro-CT enabled us to detect small, mineralized nodules that cannot be regularly detected using clinical imaging. We attempted to address this limitation and the clinical relevance of these findings by setting a threshold to report on nodules of sufficient size that likely can be detected using current imaging protocols. Future studies are needed to apply this scoring system to clinical CT scans to explore the connection between intra-articular involvement and CVJ bridging and the relationship to the continuum of DISH pathogenesis.

The advantage of micro-CT is the ability to explore novel aspects of disease features. We acknowledge that our investigation focused on the relationship between CVJ mineralization and DISH, and that CVJ changes may also be associated with other musculoskeletal conditions. Moreover, the proposed scoring system for CVJ mineralization has yet to be validated using clinical images and may need to be refined to facilitate clinical use. The generalizability of our findings is limited by the lack of diversity in the specimens investigated in terms of race and advanced age, as well as the lack of medical information on potential clinically relevant co-morbidities. Our random sampling from the total cohort of 59 specimens improved representativeness of the sample by considering sex and the continuum of DISH. Translation to a diverse clinical sample would power further statistical analysis, improve external validity, and may provide the opportunity to ask questions about the direct implication of CVJ involvement on clinical outcomes.

In conclusion, our detailed investigation of cadaveric specimens using micro-CT demonstrates an association between CVJ mineralization and DISH. CVJ bridging was associated with DISH while intra-articular mineralization was associated throughout the continuum of the disease. Distinct mineralized nodules were detected within the CVJ space in regions with ectopic spine bridging that established the diagnosis of DISH. These findings raise intriguing questions regarding the temporal relationship between CVJ mineralization/bridging and ectopic spine bridging along the continuum of DISH, and their potential interdependence. Importantly, we suggest that CVJ mineralization may be a key feature in the pathogenesis of DISH and should be considered to support diagnosis of DISH using CT scans.

5.7 References

1. Goldthwait JE. The rib joints. New England Journal of Medicine. 1940;223(15):568-73.

2. Erwin WM, Jackson PC, Homonko DA. Innervation of the human costovertebral joint: Implications for clinical back pain syndromes. J Manipulative Physiol Ther. 2000;23(6):395-403.

3. Standring S, Gray H. Gray's anatomy: The anatomical basis of clinical practice. Forty-second edition ed. Amsterdam: Elsevier; 2021.

4. Saker E, Graham RA, Nicholas R, et al. Ligaments of the costovertebral joints including biomechanics, innervations, and clinical applications: A comprehensive review with application to approaches to the thoracic spine. Cureus. 2016;8(11):e874.

5. Hansen JT, Netter FH. Netter's clinical anatomy. 4th edition. ed. Philadelphia, PA: Elsevier; 2019.

6. Cohen MJ, Ezekiel J, Persellin RH. Costovertebral and costotransverse joint involvement in rheumatoid arthritis. Ann Rheum Dis. 1978;37(5):473-5.

7. Bywaters EG. Thoracic intervertebral discitis in rheumatoid arthritis due to costovertebral joint involvement. Rheumatol Int. 1981;1(2):83-97.

8. Sales JR, Beals RK, Hart RA. Osteoarthritis of the costovertebral joints: The results of resection arthroplasty. J Bone Joint Surg Br. 2007;89(10):1336-9.

9. Ellrodt A, Goldberg D, Oberlin F, et al. Erosive arthritis of the costovertebral joint in seronegative spondyloarthropathy. J Rheumatol. 1986;13(2):452-4.

10. Chui ETF, Tsang HHL, Lee KH, et al. Mri inflammation of facet and costovertebral joints is associated with restricted spinal mobility and worsened functional status. Rheumatology (United Kingdom). 2020;59(9):2591-602.

11. Shouval A, Croitoru S, Keret S, et al. Costovertebral joint involvement in radiographic axial spondyloarthritis: A case-series computed tomography study. International Journal of Rheumatic Diseases. 2023;26(5):977-81.

12. Arroyo JF, Jolliet P, Junod AF. Costovertebral joint dysfunction: Another misdiagnosed cause of atypical chest pain. Postgraduate Medical Journal. 1992;68(802):655-9.

13. Pascual E, Castellano JA, López E. Costovertebral joint changes in ankylosing spondylitis with thoracic pain. Rheumatology. 1992;31(6):413-5.

14. Benhamou CL, Roux C, Tourliere D, et al. Pseudovisceral pain referred from costovertebral arthropathies: Twenty-eight cases. Spine. 1993;18(6):790-5.

15. Berdal G, Halvorsen S, van der Heijde D, et al. Restrictive pulmonary function is more prevalent in patients with ankylosing spondylitis than in matched population controls and is associated with impaired spinal mobility: A comparative study. Arthritis Research and Therapy. 2012;14(1).

16. Verdoorn JT, Lehman VT, Diehn FE, et al. Increased 99mtc mdp activity in the costovertebral and costotransverse joints on spect-ct: Is it predictive of associated back pain or response to percutaneous treatment? Diagn Interv Radiol. 2015;21(4):342-7.

17. Nathan H, Weinberg H, Robin GC, et al. The costovertebral joints. Anatomical-clinical observations in arthritis. Arthritis & Rheumatism. 1964;7(3):228-40.

18. Nathan H. Osteophytes of the spine compressing the sympathetic trunk and splanchnic nerves in the thorax. Spine. 1987;12(6):527-32.

19. Lipschitz M, Bernstein-Lipschitz L. Thoracic sympathetic trunk compression by osteophytes associated with arthritis of the costovertebral joint: Anatomical and clinical considerations. Cells Tissues Organs. 1988;132(1):48-54.

20. Guttentag AR, Salwen JK. Keep your eyes on the ribs: The spectrum of normal variants and diseases that involve the ribs. Radiographics. 1999;19(5):1125-42.

21. O'Bryant MW, Mahraj RP, Allen TW, et al. Rib hyperostosis: A benign entity with suspicious imaging features. Radiology Case Reports. 2022;17(9):2987-90.

22. Frager L, Heaton D, Walker CM, et al. Incidental posterior rib hyperostosis on chest ct: Incidence and etiology. Skeletal Radiology. 2022;51(6):1173-8.

23. Forestier J, Rotes-Querol J. Senile ankylosing hyperostosis of the spine. Annals of the rheumatic diseases. 1950;9(4):321-30.

24. Fournier DE, Leung AE, Battie MC, Seguin CA. Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) and early-phase DISH across the lifespan of an American population. Rheumatology 2023. doi: 10.1093/rheumatology/kead362

25. Resnick D. Degenerative diseases of the vertebral column. Radiology. 1985;156(1):3-14.

26. Sato T, Bannai T, Miyake T, et al. Two cases of severe type 2 respiratory failure associated with diffuse idiopathic skeletal hyperostosis. Annals of Geriatric Medicine and Research. 2021;25(1):55-9.

27. Ikuma H, Hirose T, Nakamura D, et al. The prevalence and characteristics of diffuse idiopathic skeletal hyperostosis (DISH): A cross-sectional study of 1519 japanese individuals. Diagnostics. 2022;12(5).

28. Slonimsky E, Lidar M, Stern M, et al. Degenerative changes of the thoracic spine do exist in patients with diffuse idiopathic skeletal hyperostosis: A detailed thoracic spine ct analysis. Acta Radiologica. 2018;59(11):1343-50.

29. Oudkerk SF, Buckens CF, Mali WPTM, et al. Diffuse idiopathic skeletal hyperostosis is associated with lower lung volumes in current and former smokers. American Journal of Respiratory and Critical Care Medicine. 2016;194(2):241-2.

30. Oudkerk SF, Hoesein FAAM, Öner FC, et al. Diffuse idiopathic skeletal hyperostosis in smokers and restrictive spirometry pattern: An analysis of the copdgene cohort. Journal of Rheumatology. 2020;47(4):531-8.

31. Fournier DE, Norley CJD, Pollmann SI, et al. Ectopic spinal calcification associated with diffuse idiopathic skeletal hyperostosis (DISH): A quantitative micro-ct analysis. Journal of Orthopaedic Research. 2019;37(3):717-26.

32. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology. 1976;119(3):559-68.

33. Kuperus JS, Oudkerk SF, Foppen W, et al. Criteria for early-phase diffuse idiopathic skeletal hyperostosis: Development and validation. Radiology. 2019;291(2):420-6.

34. Yaniv G, Bader S, Lidar M, et al. The natural course of bridging osteophyte formation in diffuse idiopathic skeletal hyperostosis: Retrospective analysis of consecutive ct examinations over 10 years. Rheumatology (United Kingdom). 2014;53(11):1951-7.

35. Kuperus JS, Buckens CF, Šprem J, et al. The natural course of diffuse idiopathic skeletal hyperostosis in the thoracic spine of adult males. Journal of Rheumatology. 2018;45(8):1116-23.

36. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.

37. Sawakami K, Watanabe K, Sato T, et al. Rib hyperostosis as a risk factor for poor prognosis in cervical spine injury patients with diffuse idiopathic skeletal hyperostosis. Spine. 2020;45(5):300-8.

38. Huang GS, Park YH, Taylor JAM, et al. Hyperostosis of ribs: Association with vertebral ossification. Journal of Rheumatology. 1993;20(12):2073-6.

39. Macones AJ, Jr., Fisher MS, Locke JL. Stress-related rib and vertebral changes. Radiology. 1989;170(1 Pt 1):117-9.

40. Ortancil O, Sarikaya S, Sapmaz P, et al. The effect(s) of a six-week home-based exercise program on the respiratory muscle and functional status in ankylosing spondylitis. Journal of Clinical Rheumatology. 2009;15(2):68-70.

41. Drăgoi RG, Amaricai E, Drăgoi M, et al. Inspiratory muscle training improves aerobic capacity and pulmonary function in patients with ankylosing spondylitis: A randomized controlled study. Clinical Rehabilitation. 2016;30(4):340-6.

42. Bağlan Yentür S, Saraç DC, Sari F, et al. The effects of pilates training on respiratory muscle strength in patients with ankylosing spondylitis. Physiotherapy Theory and Practice. 2022.

43. Broitman S, Herman A, Stern M, et al. Enthesopathy of the anterior chest wall joints in patients with diffuse idiopathic skeletal hyperostosis (DISH): A retrospective analysis of computed tomography scans. Skeletal Radiology. 2020;49(3):461-7.

44. Ibrahim AF, Darwish HH. The costotransverse ligaments in human: A detailed anatomical study. Clinical Anatomy. 2005;18(5):340-5.

45. Resnik CS, Ammann AM. Cervical spine involvement in sternocostoclavicular hyperostosis. Spine. 1985;10(9):846-8.

46. Fournier DE, Kiser PK, Beach RJ, et al. Dystrophic calcification and heterotopic ossification in fibrocartilaginous tissues of the spine in diffuse idiopathic skeletal hyperostosis (DISH). Bone Research. 2020;8(1).

Chapter 6

Discussion of Dissertation

6.1 Overview

This work presented in this dissertation leveraged two important resources. First, we established an international partnership that enabled access to electronic medical records and clinical images from a large population in Minnesota, United States (amidst the COVID-19 pandemic restrictions) through the Rochester Epidemiology Project (1, 2). The resultant studies explored a rich dataset and characterized imaging features of ectopic mineralization in the thoracic spine from female and male individuals across the lifespan. Second, we leveraged invaluable resources at the University of Western Ontario, including cadaveric specimens and access to microcomputed tomography imaging infrastructure to characterize novel imaging features of the CVJs along the continuum of DISH.

The primary purpose of this work was to better understand the continuum of DISH and its unique imaging features throughout the lifespan. We accomplished this through four major aims: i) examination of the prevalence of DISH and early-phase DISH in female and male individuals across the lifespan; ii) investigation of the current usage of terminology related to DISH by radiologists in their clinical reports; iii) exploration of the progression of imaging features related to ectopic mineralization over time and across the continuum of DISH; and iv) characterization of the relationship between pathological mineralization of the CVJs and the continuum of DISH in a sample of cadaveric specimens using microcomputed tomography.

Chapter 2 presents a retrospective study of a cross-sectional sample of computed tomography scans of the thoracic spine to evaluate the prevalence of DISH and early-phase DISH across the adult lifespan of both female and male individuals. We hypothesized that DISH would be more common than previously reported and that early-phase DISH would be prominent. Individuals over the age of 19 years who received thoracic computed tomography scans were identified and random stratified sampling by sex and age (per decade) was used. Scans from these individuals were evaluated based on established imaging criterion for both DISH and early-phase DISH and every level of the thoracic vertebral column was scored to assess the severity of ectopic bridging. We found that DISH was present in 14.2% of individuals, within a greater proportion of male (60.4%) compared to females (39.6%). Early-phase DISH was observed in 13.2% of individuals and there was no observed difference between sexes. The observed prevalence of DISH was comparable with previous reports. Our results indicated for the first time that early-phase DISH showed a prevalence similar to that of DISH. Taken together, we found that more than one in three adults over 40 years-of-age displayed imaging features of either DISH or early-phase DISH; reinforcing that this musculoskeletal condition (and its continuum) are a relevant clinical problem.

The evaluation of a large cohort of 1,600 computed tomography scans of the thoracic spine enabled us to assess the reporting of DISH by radiologists. Since the diagnosis of DISH is based on radiographic features without consideration of other features of clinical examination (e.g., physical function, subjective symptoms), we decided to explore the radiology reports associated with the images evaluated in **Chapter 3**. After image evaluation, we screened each radiology report for an *a priori* list of terms that described the phenomenon of DISH as well as imaging features of pathological mineralization. We found that radiology reports directly referenced DISH in only 24% of individuals that met the diagnostic criteria for the condition. These findings suggest an important gap in the clinical management of individuals with DISH. For example, although clinical interventions for DISH are limited, increased reporting of DISH may improve clinical outcomes by enabling clinicians to appropriately adapt their services or procedures to maximize clinical outcomes and reduce adverse events.

To understand changes in imaging features associated with DISH along its continuum, the purpose of **Chapter 4** was to identify and characterize the patterns and change in thoracic spine bridging over time. The study leveraged the results from Chapter 2 to populate three study groups with individuals that had two thoracic computed tomography scans (at least two months apart; on average, 2.7 years). Ectopic bridge scores throughout the thoracic vertebral column were compared between the first and last images in 48 individuals with DISH, 30 individuals with early-phase DISH, and 79 individuals without any phase of DISH (disease category applied based on the last scan). In individuals with new early-phase DISH (early-phase DISH only on last scan), we found that previously unaffected motion segments displayed evidence of new ectopic bridging over time. In contrast, the progression towards new DISH (DISH only on last scan) or severe DISH were characterized by increased severity of bridge scores at previous affected motion segments. Our results raise the possibility that clinical prevention or management may be critical at specific points along the continuum of DISH, and that there is likely a need for targeted interventions.

Lastly, we leveraged the invaluable resource of cadaveric specimens and access to microcomputed tomography imaging at the University of Western Ontario. Since ectopic mineralization associated with DISH is not limited to the vertebral column, a detailed characterization of the CVJs was conducted in **Chapter 5**. To do so, we developed a novel scoring system to assess the extent of ectopic bridging between the head of the rib and vertebrae and assess intra-articular mineralization. Microcomputed tomography scans of a total of 41 specimens were studied, revealing that features of CVJ bridging was 2.7 times more likely in specimens with DISH than those without a diagnosis of DISH. Interestingly, unlike vertebral bridging the side of articulation did not influence the prevalence of CVJ bridging. A novel aspect of the study was the characterization of two types of intra-articular mineralized material. First, we reported diffuse mineralized material within the CVJ that was more common in female specimens assigned to the pre-DISH group. Second, we reported distinct localized nodules that were 3.1 times more likely in CVJs from specimens with DISH than those without a diagnosis of DISH. This work suggests that the involvement of the CVJs may serve as a valuable addition to the diagnostic criteria for DISH when evaluating with computed tomography. Further, intra-articular mineralization of the CVJ may also have a role in the pathogenesis of DISH.

6.2 Significance of findings and directions for future research

Based on our findings of the prevalence of DISH and its continuum in a population in America, we can predict that 7.3 million Canadians (2.3 million female, 5.0 million males) over 40 years of age may be living with DISH or early-phase DISH. While the medical resources used by individuals with DISH are unknown, it is clear that risk factors associated with DISH continue to be more prevalent in society (e.g., increased life expectancy, prevalence of diabetes and obesity, sedentary lifestyles). Our findings from Chapters 2 and 3 suggest that DISH may be underreported. We are confident that a better understanding of the continuum of DISH will facilitate future research and clinical observation that will improve outcomes for people living with this common yet poorly understood musculoskeletal condition.

6.2.1 Implications for clinical practice

The clinical implications of DISH remain an area of insufficient investigation and knowledge (3). Despite the notable prevalence of this musculoskeletal condition reported in Chapter 2, clinicians are often under-reporting it (Chapter 3). This may be attributed to the current lack of disease modifying treatments to alter clinical prognosis following a clinical diagnosis (3). This cycle needs to be disrupted by well-designed controlled clinical research that examines the connection between objective imaging features and the clinical experience of DISH. This can be achieved by improving the generalizability of both the criteria for DISH and early-phase DISH to enhance routine clinical detection, observation of clinical features, and the ability to recruit for future studies through electronic medical records/coding systems (e.g., International Statistical Classification of Diseases and Related Health Problems, electronic medical records). For example, our findings of 13.2% prevalence of early-phase DISH (202 individuals) inspire an exciting opportunity to design longitudinal, prospective studies that monitor symptoms and change over time. In turn, this would enable—for the first time—valuable prognostic information for both people living with DISH and clinicians providing care.

Currently, the description of general spine stiffness with or without back pain are insufficient to establish a clinical profile to diagnose DISH based on symptoms. To date, DISH has only been associated to general features of poor health (e.g., diabetes mellitus, dyslipidemia, and hypertension) (3). Identifying clinical features unique to DISH may result from enhancing the characterization of imaging features beyond the current criteria of three contiguous completed bridges across the vertebral column. Given the heterogenous pathological changes associated with DISH, as demonstrated in this dissertation and previous studies, we propose that our clinical understanding of DISH would be improved by reliable subgrouping. Similar to the clinical classification system used with ossification of the posterior longitudinal ligament (4), we postulate that groups such as extensive bridging in only one region of the vertebral column, multiple sites of segmental bridging, or multiple sites of independent bridging could be clinically relevant in the clinical characterization of DISH. In turn, further understanding of the continuum of imaging features will likely highlight the need for targeted interventions at different stages, as our results in Chapter 4 suggest. Based on the current unmet clinical need, it is logical that interventions focused on preventing the formation of ectopic bridges are most useful early in the continuum of early-phase DISH and DISH. Whereas, interventions that delay or halt the progression of ectopic bridging are valuable for individuals already diagnosed with DISH, which may be achieved through exercise programs that promote spinal mobility (5). Interestingly, the association of the CVJ mineralization with DISH indicates a novel and extremely valuable opportunity to screen, evaluate, monitor, and/or improve respiratory function for people living with DISH.

Lastly, we speculate that a shift away from reliance on computed tomography findings may benefit the characterization of unique clinical features associated with DISH. One study by Dr. Reuven Mader in 2010 applied the 18 specific tender points (typically used to assess people with fibromyalgia) with a cohort of individuals with DISH and revealed a lower pain threshold compared to individuals without DISH, which indicates potential changes in nervous system sensitization (6). Subsequent clinical studies implementing other physical clinical measures have not been published. Recently, components of physical function (e.g., grip strength, one-leg standing time, sit-and-reach, functional reach) are being explored in clinical investigations focused on DISH which facilitates further research by transdisciplinary research teams (7, 8). The development of readily accessible tools that facilitate evaluation of the whole person during clinical examination may include the use of ultrasound to view multiple peripheral entheseal sites (9, 10). Also, the symptoms likely associated with DISH (physical disability and back pain) align with referral for magnetic resonance imaging compared to computed tomography. Previously studies have implemented magnetic resonance imaging to assess imaging features of DISH and may enable investigation of additional clinical features like inflammation at the base of an osteophyte or in its soft tissue surrounding (11). Imaging protocols commonly used for indications of low back pain general capture lower thoracic motions segments in addition to the lumbar vertebral column and could be a rich dataset to explore in the future. For example, it may be useful to leverage previous scans involving the lower thoracic regions of T9-12 to: i) conduct additional research focused on associating clinical symptoms with features of ectopic spine mineralization, and ii) determine at the individual if DISH contributes to symptoms that would guide a particular clinical pathway. A portable modality such as digital radiography may also prove useful to implement screening programs.

6.2.2 Need for an improved clinical imaging criteria

The current gold-standard for the diagnosis of DISH remains the radiographic imaging features described by Resnick and Niwayama in 1976 (12). In this criteria, the lack of degenerative or structural changes within the sacro-iliac and zygapophyseal joints are highlighted as key features to differentiate from other pathologies of the vertebral column; most notably, ankylosing spondylitis. Given the accessibility and advancement in the application of computed tomography, it is regularly used in current studies to investigate the prevalence and pathogenesis of DISH; however, a focus on early detection and extraspinal involvement remains rare. Based on the work in the present dissertation and studies that used computed tomography, it is clear that degenerative changes throughout the vertebral column are common in people with DISH (13).

Since the establishment of these diagnostic criteria nearly 50 years ago, various modifications have been proposed that reduce the emphasis on the number of contiguous vertebral bridges and include detection of extraspinal features (14). Despite its name (i.e., “diffuse” idiopathic skeletal hyperostosis), the primary diagnostic feature of DISH continues to be changes in the vertebral column. Mineralization at the calcaneus, pelvis, tarsals, metacarpals, olecranon, patella, and glenohumeral, shoulder, knees, and elbows have been described as regularly involved in DISH (15, 16). Our investigation of the CVJ exemplifies that ectopic mineralization can simultaneously occur in other joints in specimens with DISH, supporting the idea that evaluation of peripheral joints has value to understand the entire experience of living with DISH. In fact, we believe that the CVJs should be evaluated in the assessment of DISH when using computed tomography. This idea is largely supported by our findings in Chapter 5 that reported a strong association between the prevalence and severity of CVJ bridging and DISH, as well as within motion segments with active DISH. Ultimately, the clinical features of DISH as a distinct entity need to be reconsidered given the historical predilection that it is a systemic condition, although it is not currently evaluated as such.

We believe that the results from our studies of the continuum of DISH advocate for a modified approach that looks beyond contiguous bridging as the primary diagnostic feature and instead evaluates the pattern of ectopic mineralization within an individual. While it is generally accepted that the presentation of three contiguous complete bridges of the anterolateral aspect of the vertebral bodies represents a definitive phenotype of DISH, the heterogeneity in imaging features observed throughout the continuum of DISH suggests the opportunity for disease subgrouping. Fortunately, recent early-phase criterion based on ectopic bridge scores at each independent motion segment has advanced the field to appreciate the continuum of DISH (17). One concern is the continued focus on the relationship between contiguous motion segments. Once three contiguous bridges are established to fulfill the diagnostic criteria for DISH, there is little characterization of the progressive nature of the disease. For example, it is unknown whether clinical symptoms differ between individuals that present with the minimal threshold of three contiguous bridges compared to another with significantly greater involvement of the vertebral column. The immediate clinical value of scoring each motion segment is unclear and it is likely unreasonable to expect radiologists to implement into routine practice. At this time, scoring is most important to researchers and those with a specific interest in DISH. Perhaps modification of the diagnostic criteria for DISH based on computed tomography scans that highlights both early phases of the condition and progressive change over time is needed to inspire greater reporting in the clinic. We are in favor of a strategy that evaluates all phases of bridging throughout the thoracic vertebral column to best categorize phenotypes of DISH and enable important monitoring of progression.

6.2.3 Sex-related difference in DISH

In the present dissertation, sex-related differences were specifically investigated for the overall prevalence of DISH as well as in our study of the CVJs. Our findings align with the previously reported male predominance of DISH (ratio of ~2:1 compared to females). The historical reporting of DISH as a disease of male individuals has created a bias in some research that disregards the experiences of female individuals. Our studies contribute three overarching findings specific to the role of sex in DISH. First, the prevalence of DISH is less among female individuals compared to males. Second, among both sexes the prevalence of DISH increases with advanced age. Third, male individuals displayed more complete bridging of the vertebral column compared to females; however, female individuals regularly display more features of early-phase bridging. It is possible that the differences in pathological mineralization between sexes could be related to natural hormones and their fluctuation over time. A study of 1,545 postmenopausal women indicated that DISH was associated with increased events of vertebral fracture, greater lumbar bone density, and significantly degraded trabecular bone scores compared to without DISH (18). Interestingly, there is mixed data on the relationship between bone mineral density and DISH in the published literature (19-24). Although, it is well established that both sexes with DISH are at increased risk for vertebral fracture (19, 25-27).

Our characterization of the severity of ectopic bridge scores did not display a significant difference based on sex; implying that the objective scoring of DISH is consistent between sexes despite the difference in disease prevalence. It seems that male individuals are affected more with DISH and not that the severity of the condition is greater among males. Therefore, it is feasible that different environmental exposures, societal roles, or occupations linked to sex may explain the observed sex difference. For example, previous research has shown that occupations with manual labor and heavy lifting were associated with pathological involvement of ectopic mineralization in joints (28, 29). It is possible that male-dominated professions may result in greater exposure to either traumatic or repetitive spine trauma that contributes to the pathogenesis of DISH. Our findings ultimately underscore that pathological mineralization associated with DISH is not exclusive to male individuals but does occurs more often (ratio of ~2:1 compared to females). As such, we argue that inclusion of sex is a requirement for studies focused on the pathogenesis of DISH to better understand the differences in etiology and potential pathogenesis.

6.2.4 Disease pathogenesis

Our data adds new insight to the mystery of the pathogenesis of this idiopathic musculoskeletal condition. The observation of localized nodules of mineralized material detected on computed tomography within the intervertebral disc (Chapter 4) and the CVJ (Chapter 5) in DISH inspires a theory that localized nodules could be a possible precursor to the formation of complete bridges between vertebral bodies as well as the across the CVJ. These findings resemble the pathological changes of dystrophic calcification described in human intervertebral discs with DISH (30). Given the prevalence of these localized nodules across the continuum of DISH, especially in individuals meeting the early-phase criteria, specimens assigned to pre-DISH, and localization to regions with DISH disease activity, it reasons that these localized nodules contribute to the pathogenesis of disease onset. Future studies that document the prevalence and monitor the progress of these localized nodules with repeated imaging would further support this hypothesis.

6.3 Limitations of the described research

Imaging features are the primary clinical feature associated with DISH, which is typically limited to advanced stages of the condition (i.e., three contiguous complete bridges in the spine) (12). Our work addressed this limitation in the field by exploring the continuum of DISH through an objective evaluation using a validated scoring system of ectopic vertebral bridging (17). It is important to acknowledge however that the four-point scoring system used to assess ectopic bridging is effective to evaluate the dichotomous extremes (i.e., no bridging and complete bridging). There is however tremendous heterogeneity in the appearance of complete bridging that is not effectively captured with this scoring system. The first computed tomography-based scoring system proposed to assess vertebral bridging was based on seven distinct levels and better characterized features of early or intermediate phases of ectopic bridging (31). We also acknowledge that our development and use of a novel scoring system for CVJ bridging requires subsequent validation for application in other research, particularly studies using clinical imaging protocols. Future work may consider defining more levels of ectopic bridging to precisely score the extent of pathological involvement, as well as other characteristics such as the angle, volume, density, or direction of bridging.

We acknowledge that DISH has been reported all regions of the vertebral column and decided to focus on thoracic computed tomography given the established predominance of involvement in this region. As a result, the sacro-iliac joints were not available for evaluation. This limitation is important to acknowledge since lack of involvement of the sacro-iliac joints is one component of Resnick and Niwayama's diagnosis criteria for DISH that differentiates from ankylosing spondylitis. To address this limitation, we carefully examined the zygapophyseal joints for evidence of structural changes including erosion, sclerosis, or bony fusion. It is also worth noting that our focus on computed tomography scans enabled detailed investigation of the imaging features of pathological mineralization, yet also biased our selection to individuals that received imaging over the past decade (since computed tomography has become more accessible and used routinely in standard practice). There would be tremendous benefit to examining changes in other spinal and extraspinal structures in future work using various imaging modalities and imaging protocols that may capture the vertebral column (e.g., whole body or chest imaging).

Our work was limited to retrospective study designs and sampling from specific populations. With the Rochester Epidemiology Project, the population was predominantly white, from the geographic area of Olmsted County, and individuals most often received imaging of the thoracic vertebral column for reason related to trauma. Our stratified random sampling aimed to enhance the representativeness of our results by exploring imaging features across the lifespan and sex. We acknowledge that further studies are desperately needed to better understand the impact of geography, race, and ethnicity on the prevalence and clinical features of DISH. Further, our study of cadaveric specimens posed a similar limitation since donors were also white, from the geographic area of Southwestern Ontario, and of advanced age with unknown co-morbidities (since medical history was not available). Despite these limitations, our work was critical to generate new questions and hypotheses for future studies that will advance the field of DISH research.

6.4 Conclusions

This dissertation employed an established population-based dataset to explore timely questions related to DISH prevalence and progression of imaging features, reporting by radiologists, and relationship with CVJ mineralization using microcomputed tomography imaging. New information was gained regarding the prevalence and changes in imaging features along the continuum of DISH in female and male individuals across the lifespan. While there is a greater prevalence of DISH among male individuals, our results indicate that the imaging features and progression over time are not different between sexes. Importantly, this underscores the need to include all sexes in studies of DISH pathogenesis. Our examination of the CVJ inspires evaluation of the clinical implication of the mineralization of these joints (among other extraspinal changes) in individuals with DISH. Ultimately, we highlight that DISH is a significant clinical problem and that the current clinical awareness can be improved. The most valuable future work will aim to link the observed imaging features with the lived experience of DISH and its continuum.

6.5 References

1. Rocca WA, Yawn BP, St Sauver JL, et al. History of the rochester epidemiology project: Half a century of medical records linkage in a us population. Mayo Clin Proc. 2012;87(12):1202-13.

2. St Sauver JL, Grossardt BR, Yawn BP, et al. Data resource profile: The rochester epidemiology project (rep) medical records-linkage system. Int J Epidemiol. 2012;41(6):1614-24.

3. Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: Clinical features and pathogenic mechanisms. Nature Reviews Rheumatology. 2013;9(12):741-50.

4. Matsunaga S, Sakou T. Ossification of the posterior longitudinal ligament of the cervical spine: Etiology and natural history. Spine. 2012;37(5):E309-E14.

5. Al-Herz A, Snip JP, Clark B, et al. Exercise therapy for patients with diffuse idiopathic skeletal hyperostosis. Clinical rheumatology. 2008;27(2):207-10.

6. Mader R, Novofastovski I, Rosner E, et al. Nonarticular tenderness and functional status in patients with diffuse idiopathic skeletal hyperostosis. Journal of Rheumatology. 2010;37(9):1911-6.

7. Banno T, Togawa D, Hasegawa T, et al. The controlled study of diffuse idiopathic skeletal hyperostosis for the assessment of physical function in elderly populations. Journal of Orthopaedic Science. 2018;23(6):929-34.

8. Li S, Banno T, Hasegawa T, et al. Long-term effects of diffuse idiopathic skeletal hyperostosis on physical function: A longitudinal analysis. Journal of Orthopaedic Science. 2023.

9. Mader R, Novofastovski I, Iervolino S, et al. Ultrasonography of peripheral entheses in the diagnosis and understanding of diffuse idiopathic skeletal hyperostosis (DISH). Rheumatology International. 2015;35(3):493-7.

10. Mader R, Novofastovski I, Iervolino S, et al. Can ultrasonography of peripheral entheses play a role in the diagnosis and understanding of diffuse idiopathic skeletal hyperostosis (DISH)? Arthritis and Rheumatology. 2014;66(SUPPL. 10):S59.

11. Eshed I. Is there a place for magnetic resonance imaging in diffuse idiopathic skeletal hyperostosis ? Clinical role of mri in DISH. Exploration of Musculoskeletal Diseases. 2023;1(2):43-53.

12. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology. 1976;119(3):559-68.

13. Slonimsky E, Lidar M, Stern M, et al. Degenerative changes of the thoracic spine do exist in patients with diffuse idiopathic skeletal hyperostosis: A detailed thoracic spine ct analysis. Acta Radiologica. 2018;59(11):1343-50.

14. Kuperus JS, de Gendt EEA, Oner FC, et al. Classification criteria for diffuse idiopathic skeletal hyperostosis: A lack of consensus. Rheumatology (United Kingdom). 2017;56(7):1123-34.

15. Resnick D, Shaul SR, Robins JM. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier's disease with extraspinal manifestations. Radiology. 1975;115(3):513-24.

16. Mader R, Sarzi-Puttini P, Atzeni F, et al. Extraspinal manifestations of diffuse idiopathic skeletal hyperostosis. Rheumatology. 2009;48(12):1478-81.

17. Kuperus JS, Oudkerk SF, Foppen W, et al. Criteria for early-phase diffuse idiopathic skeletal hyperostosis: Development and validation. Radiology. 2019;291(2):420-6.

18. Pini SF, Pariente E, Olmos JM, et al. Diffuse idiopathic skeletal hyperostosis (DISH) and trabecular bone score (tbs) in postmenopausal women: The camargo cohort. Semin Arthritis Rheum. 2023;61:152217.

19. Diederichs G, Engelken F, Marshall LM, et al. Diffuse idiopathic skeletal hyperostosis (DISH): Relation to vertebral fractures and bone density. Osteoporosis International. 2011;22(6):1789-97.

20. Westerveld LA, Verlaan JJ, Lam MGEH, et al. The influence of diffuse idiopathic skeletal hyperostosis on bone mineral density measurements of the spine. Rheumatology. 2009;48(9):1133-6.

21. Eser P, Bonel H, Seitz M, et al. Patients with diffuse idiopathic skeletal hyperostosis do not have increased peripheral bone mineral density and geometry. Rheumatology (Oxford, England). 2010;49(5):977-81.

22. Sethi A, Ruby JG, Veras MA, et al. Genetics implicates overactive osteogenesis in the development of diffuse idiopathic skeletal hyperostosis. Nat Commun. 2023;14(1):2644.

23. Uehara M, Takahashi J, Ikegami S, et al. Differences in bone mineral density and bone turnover markers between subjects with and without diffuse idiopathic skeletal hyperostosis. Spine. 2020;45(24):E1677-E81.

24. Kuperus JS, Samsour L, Buckens CF, et al. Bone mineral density changes over time in diffuse idiopathic skeletal hyperostosis of the thoracic spine. Bone. 2018;112:90-6.

25. Caron T, Bransford R, Nguyen Q, et al. Spine fractures in patients with ankylosing spinal disorders. Spine. 2010;35(11):E458-E64.

26. Westerveld LA, Van Bemmel JC, Dhert WJA, et al. Clinical outcome after traumatic spinal fractures in patients with ankylosing spinal disorders compared with control patients. Spine Journal. 2014;14(5):729-40.

27. Okada E, Yoshii T, Yamada T, et al. Spinal fractures in patients with diffuse idiopathic skeletal hyperostosis:A nationwide multi-institution survey. Journal of Orthopaedic Science. 2019;24(4):601-6.

28. Macones AJ, Jr., Fisher MS, Locke JL. Stress-related rib and vertebral changes. Radiology. 1989;170(1 Pt 1):117-9.

29. Mata S, Fortin PR, Fitzcharles M-A, et al. A controlled study of diffuse idiopathic skeletal hyperostosis. Medicine (Baltimore). 1997;76(2):104-17.

30. Fournier DE, Kiser PK, Beach RJ, et al. Dystrophic calcification and heterotopic ossification in fibrocartilaginous tissues of the spine in diffuse idiopathic skeletal hyperostosis (DISH). Bone Research. 2020;8(1).

31. Yaniv G, Bader S, Lidar M, et al. The natural course of bridging osteophyte formation in diffuse idiopathic skeletal hyperostosis: Retrospective analysis of consecutive ct examinations over 10 years. Rheumatology (United Kingdom). 2014;53(11):1951-7.

Appendix

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Expected publication date	Aug 2023
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Title	Imaging features characterizing the continuum of Diffuse Idiopathic Skeletal Hyperostosis (DISH)
Institution name	The University of Western Ontario
Expected presentation date	Aug 2023
Portions	Full text as a thesis chapter.
Requestor Location	[redacted] London, ON N6H 5G7 Canada Attn: Dale Fournier
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Appendix B. Copyright permission agreement with Oxford University Press

20-000640 - A study has been deemed Exempt by the IRB

IRBe <[redacted]>
Wed 2020-02-12 11:40
To: [redacted] <[redacted]>

Principal Investigator Notification:

From: Mayo Clinic IRB
To: [redacted]
CC: [redacted]

Re:
IRB Application #: 20-000640

Title: Understanding the spatiotemporal progression of diffuse idiopathic skeletal hyperostosis using repeated spine imaging in a longitudinal sample from Olmsted county, MN, United States

IRBe Protocol Version: 0.01
IRBe Version Date: 1/20/2020 3:27 PM

IRB Approval Date: 2/12/2020
IRB Expiration Date:

The above referenced application was reviewed by expedited review procedures and is determined to be exempt from the requirement for IRB approval (45 CFR 46.104d, category 4). Continued IRB review of this study is not required as it is currently written. However, requests for modifications to the study design or procedures must be submitted to the IRB to determine whether the study continues to be exempt.

The Reviewer approved waiver of HIPAA authorization in accordance with applicable HIPAA regulations.

AS THE PRINCIPAL INVESTIGATOR OF THIS PROJECT, YOU ARE RESPONSIBLE FOR THE FOLLOWING RELATING TO THIS STUDY.
1) When applicable, use only IRB approved materials which are located under the documents tab of the IRBe workspace. Materials include consent forms, HIPAA, questionnaires, contact letters, advertisements, etc.
2) Submission to the IRB of any modifications to approved research along with any supporting documents for review and approval prior to initiation of the changes.
3) Submission to the IRB of all Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) and major protocol violations/deviations within 5 working days of becoming aware of the occurrence.
4) Compliance with applicable regulations for the protection of human subjects and with Mayo Clinic Institutional Policies.

Appendix C. Ethics approval from Mayo Clinic

[EXTERNAL] Study 008-OMC-20: Understanding the spatiotemporal progression of diffuse idiopathic skeletal hyperostosis using repeated spine imaging in a longitudinal sample from Olmsted County, MN United States

[redacted]

Thu 2020-02-20 10:48

To: [redacted] <[redacted]>

Cc: [redacted] <[redacted]>; [redacted] <[redacted]>

OLMSTED MEDICAL CENTER
INSTITUTIONAL REVIEW BOARD

February 20, 2020

RE: OMC Study # 008-OMC-20

The Executive Committee of the Olmsted Medical Center Institutional Review Board has approved your study entitled Understanding the spatiotemporal progression of diffuse idiopathic skeletal hyperostosis using repeated spine imaging in a longitudinal sample from Olmsted County, MN United States.

The investigator is reminded that no records may be accessed for this study for participants who have declined authorization for use of their medical records in research.

This approval is valid for one year, unless the IRB determines that it is appropriate to halt or suspend the study earlier. A stamped IRB approved protocol will be sent in a separate email.

Please note that any changes to the study as approved must be promptly reported and approved.

[redacted], M.D., Chair
Olmsted Medical Center Institutional Review Board
< br>

Appendix D. Ethics approval from Olmsted Medical Center

Schulich
MEDICINE & DENTISTRY

October 29, 2018

Use of Cadaveric Material – Ethics Approval Notice

Principal Investigator: Dr. Cheryle Seguin
Review level: Cadaveric Research Ethics Board
Approval Number specimens: ~100 fixed cadaveric spine specimens
Protocol Title: Investigation of pathological calcification of spinal tissues
Department & Institution: Western
Ethics Approval Date and Number: 10292018

Documents Reviewed and Approved & Documents Received for Information:

ACB Use of Cadaveric Material for Research Purposes Research Proposal Submission – Appendix I
Request for Photography/Videography – Appendix III
Version: 1

This is to notify that the University of Western Ontario Subcommittee for Cadaveric Material Research Ethics has approved your request as indicated by the approval date and number listed above.

The ethics approval for this study shall remain valid for one year, at which time the PI must submit a study completion form or contact the cadaveric material subcommittee Chair (or designate signed below) for an extension or amendments.

[redacted]

Signature

Schulich School of Medicine & Dentistry, Western University, Building, Rm. 491
1511 Richmond St. London, ON, Canada N6A 5C1
t. 519.661.2111 ext. 86756 www.schulich.uwo.ca

Western

Appendix E. Ethics approval notice for use of cadaveric material

Curriculum vitae of Ph.D.

Date:	2023-08-11
Name:	Dale E. Fournier
Post-secondary Education and Degrees:	The University of Western Ontario London, Ontario, Canada 2020-2022 M.PT. 2018-2023 Ph.D.
Competitive Scholarships:	Young Investigator Award, Bone and Joint Institute 2022-2023 Ontario Graduate Scholarship 2020-2021; 2021-2022; 2022-2023 Arthritis Society Graduate Ph.D. Award 2019-2022 Transdisciplinary Ph.D. Training Award, Bone and Joint Institute 2018-2019; 2019-2020; 2020-2021; 2021-2022
Awards:	Best Presenter Award Canadian Arthritis Research Conference, 2023 Graduation Award, Oncology Division Canadian Physiotherapy Association, 2022 Dr. Suzanne Bernier Award in Skeletal Biology 2022 Top Graduate Student Poster Award Canadian Arthritis Research Conference, 2020 Graduate Student Teaching Award Society of Graduate Students, 2019
Related Work Experience	Graduate Teaching Assistant The University of Western Ontario Fall 2022 (x2 concurrent positions) Fall 2019, Winter 2020 Fall 2018, Winter 2019

Publications:

2023

Fournier DE, Leung AE, Battié MC, Séguin CA. (2023). Prevalence of Diffuse Idiopathic Skeletal Hyperostosis (DISH) and Early-phase DISH Across the Lifespan of an American Population. Rheumatology. https://doi.org/10.1093/rheumatology/kead362

Fournier DE, Veras MA, Brooks CR, Quinonez D, Millecamps M, Stone LS, Séguin CA. (2023). Stiffness and Axial Pain are Associated with the Progression of Calcification in a Mouse Model of Diffuse Idiopathic Skeletal Hyperostosis. Arthritis Research & Therapy, 25, 72. https://doi.org/10.1186/s13075-023-03053-3

2021

Fournier DE, Beaucage KL, Beach RJ, Kiser PK, Séguin CA, Dixon SJ. (2021). Ectopic mineralisation of the mandibular symphysis in ENT1 knockout mice: A model of dystrophic calcification. Bone Reports, 15, 101100. https://doi.org/10.1016/j.bonr.2021.101100

Fournier DE, Groh AMR. (2021). A Pilot Study of a Physical Therapy Cadaveric Anatomy Course: Assessing the Impact of Examination Format on the Learning Environment. Anatomical Sciences Education, 14(3), 351-360. https://doi.org/10.1002/ase.2011

Groh AMR, **Fournier DE**, Battié MC, Séguin CA. (2021). Innervation of the Human Intervertebral Disc: A Scoping Review. Pain Medicine, 22(6), 1281-1304. https://doi.org/10.1093/pm/pnab070

2020

Fournier DE, Kiser PK, Shoemaker JK, Battié MC, Séguin CA. (2020). Vascularization of the Human Intervertebral Disc: A Scoping Review. JOR Spine, 3(4), e1123. https://doi.org/10.1002/jsp2.1123

Fournier DE, Kiser PK, Beach RJ, Dixon SJ, Séguin CA. (2020). Dystrophic Calcification and Heterotopic Ossification in Fibrocartilaginous Tissues of the Spine in Diffuse Idiopathic Skeletal Hyperostosis (DISH). Bone Research, 8, 16. https://doi.org/10.1038/s41413-020-0091-6

Fournier DE, Groh AMR, Nair SM, Norley CJD, Pollmann SI, Holdsworth DW, Power NE, Beveridge T. (2020). Microcomputed Tomography Is a Precise Method That Allows for Topographical Characterization of Lymph Nodes and Lymphatic Vessels. Lymphatic Research and Biology, 18(2), 166-173. https://doi.org/10.1089/lrb.2019.0007