Diffuse idiopathic skeletal hyperostosis (DISH)

The impact of spinal ankylosis on trauma patients

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Cover design and lay out
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Printed by
ZuidamUithof Drukkerijen - Utrecht

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Diffuse idiopathic skeletal hyperostosis (DISH)

De invloed van spinale ankylose op traumapatiënten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 24 november 2011 des middags te 4.15 uur

door

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geboren op 1 maart 1981 te Warnsveld

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Financial support by the AO Research Fund of the AO Foundation (project no. S-07-20V) was gratefully acknowledged.

This thesis is based upon the following publications

LA Westerveld, JJ Verlaan, WJA Dhert, FC Öner
Management of Fractures of the Ankylosed Spine
In press *European Musculoskeletal Review*

LA Westerveld, JJ Verlaan, FC Öner
Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications
Eur Spine J 2009;18:145 – 56

LA Westerveld, HME Quarles van Ufford, JJ Verlaan, FC Öner
The prevalence of diffuse idiopathic skeletal hyperostosis in an outpatient population in the Netherlands
J Rheumatol 2008;35:1635 – 8

JJ Verlaan, **LA Westerveld**, JW van Keulen, RLAW Bleys, WJA Dhert, JA van Herwaarden, FL Moll, FC Öner
Quantitative analysis of the anterolateral ossification mass in diffuse idiopathic skeletal hyperostosis of the thoracic spine
Eur Spine J 2011;20:1474 – 9

LA Westerveld, JJ Verlaan, MGEH Lam, WP Scholten, RLAW Bleys, WJA Dhert, FC Öner
The influence of diffuse idiopathic skeletal hyperostosis on bone mineral density measurements of the spine
Rheumatology (Oxford) 2009;48:1133 – 6

LA Westerveld, JC van Bemmel, WJA Dhert, FC Öner, JJ Verlaan
Clinical outcome after spinal fractures in patients with ankylosing spinal disorders compared to control patients
Submitted for journal publication

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CHAPTER 1

General introduction on diffuse idiopathic skeletal hyperostosis and outline of this thesis

Adapted from:
Management of fractures of the ankylosed spine

LA Westerveld
JJ Verlaan
WJA Dhert
FC Öner

In press *European Musculoskeletal Review*

Diffuse idiopathic skeletal hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) is a common but often underestimated systemic disorder of the axial and appendicular skeleton, in which ossification of various ligaments and entheses occurs. The most prominent feature of DISH is flowing ossification at the anterolateral aspect of the thoracic spine, often compared to melting candle wax. Although the term DISH itself was not introduced until the 1970s, its characteristic ossifying diatheses have been demonstrated in human remains found in archeological sites all over the world dating back as far as the Stone Age. For example, the remains of Shanidar I, a Neanderthal who lived approximately 50,000 years ago in northern Iraq, showed large flowing osteophytes in the lumbar spine, on both calcaneal tuberosities, both patellae and the left olecranon.[39] Comparable anomalies have been described in a female individual who lived in Montescaglioso, southern Italy, 6,000 years BC.[30] Even though the diagnosis of ankylosing spondylitis (AS) was initially assigned to the mummified remains of the Egyptian pharaoh Ramses II (1302 – 1213 BC), critical re-appraisal of the radiographic material of his skeleton suggested the diagnosis DISH to be more appropriate.[33;56]

Figure 1
Official portrait of Ferdinand I de' Medici (1549 - 1609) as Cardinal, showing evident obesity. Permission to publish Polo Museale Fiorentino.

In more recent history, several male members of the de' Medici family, the richest, most powerful rulers of Florence in the Italian renaissance, were claimed to have DISH. The skeletons of the Grand Dukes Cosimo I (1519 – 1574) and his son Ferdinando I (1549 – 1609) demonstrated extensive ossifications of the thoracic spine as well as enthesopathies in several ligament and tendon attachments. Both individuals were (morbidly) obese at the end of their lifetime, as is attested by several written and artistic sources (figure 1).[70;231] The lifestyle of the Dukes was characterized by a diet high in saturated fats but low in vegetables, larded with wine and beer, in combination with a sedentary life without much exercise. This elite lifestyle was not only characteristic for individuals of high status, but shows much resemblance with the 'monastic way of life' of medieval monks in London (England) and Maastricht (the Netherlands); whose excavated remains also showed extensive alterations due to DISH.[180;229] The German writer, poet and drawer Johann Wolfgang von Goethe (1749 – 1832) was diagnosed post-mortem with spinal ankylosis due to DISH; which may have caused his characteristic rigid posture and typical stiff gait.[222]

DISH is not confined to human beings, however, its presence has been demonstrated in many pre-historic animal species. For instance in the saber-toothed cat; a carnivore about the same size, but heavier built than the African lion we know today.[17] Additionally, the remains of Menoceras (early rhinoceros), Protolabis (early camel) and Equus sp. (early horse) showed features of DISH in the spine as well as peripheral ligamentous, tendon or capsule insertion ossifications. These ossifications were primarily detected in fossils that were demonstrated to be of older age, based on tooth wear patterns. Sings of DISH have even been described in dinosaurs.[183] DISH has occasionally been described in modern-day dogs; predominantly in the Boxer breed.[150;239]

Table 1
Synonyms for DISH.

Spondylitis deformans[110]
Spondylitis ossificans ligamentosa[158]
Senile vertebral ankylosing hyperostosis (also known as Forestier's disease)[65]
Spondylosis hyperostotica[160]
Physiologic vertebral ligamentous calcification[201]
Generalized juxta-articular ossifications of vertebral ligaments[210]
Vertebral hyperostosing discosomatic osteoarthritis[16]
Ankylosing hyperostosis[28]
Diffuse idiopathic skeletal hyperostosis[179]
Diffuse enthesopathic hyperostosis[114]

Diagnosis

Over the years DISH has been described under a variety of names (table 1). Although the disorder presently known as DISH has been identified in medical literature as early as the 19th century, Forestier and Rotes-Querol were the first to comprehensively describe the clinical and radiological features of the disease in 1950.[65] After their thorough exam of nine male patients and two anatomical specimens they wrote: 'Our attention has been drawn to an ankylosing disease of the spine developing in old people, with a painless onset and clinical, pathological, and radiological features distinguishing it from ankylosing spondylitis.'
They named this new entity *senile vertebral ankylosing hyperostosis*; since its most striking pathological element was hyperostosis and its two constant clinical features were spinal rigidity and advanced age. A flowing continuous bony protuberance alongside the anterolateral aspect of the thoracic spine was observed, following the shape of the spine and grooved by blood vessels originating from the aorta. The ossifications were more prominently located on the right side of the spine, contralateral from the descending aorta. In the lumbar spine they described the outgrowths to be more discontinuous, shaped like candle-flames. The predilection for right-sided involvement they observed in the thoracic spine was not so obvious in the lumbar region, especially below the bifurcation of the aorta.

It was not until 1975 that Resnick and coworkers emphasized the extraspinal manifestations of the disorder often coexisting with the spinal ossifications; which were frequently encountered in pelvis, tarsal bones, ulnar olecranon and patella.[179] Based on these findings they suggested the name *diffuse idiopathic skeletal hyperostosis*, commonly abbreviated as DISH, to be more appropriate; stressing the fact that hyperostosis could be localized at virtually all places in the skeleton (due to an unknown cause). Resnick and Niwayama were also the first to propose specific radiological diagnostic criteria, which are still in use today (figure 2):[178]

1. The presence of flowing calcification and ossification along the anterolateral aspect of at least four contiguous vertebral bodies, with or without associated localized pointed excrescences at the intervening vertebral body-intervertebral disc junctions.
2. A relative preservation of intervertebral disc height in the involved area and the absence of extensive radiographic changes of 'degenerative' disc disease, including vacuum phenomena and vertebral body marginal sclerosis.
3. The absence of apophyseal joint bony ankylosis and sacroiliac joint erosion, sclerosis, or bony fusion.

Criterion 1 required ossification of four contiguous vertebral bodies to establish the diagnosis of DISH; a number that was arbitrarily chosen, but included to distinguish DISH from spondylosis deformans. Criterion 2 was introduced to distinguish DISH from degenerative disease of the intervertebral disc (IVD) and criterion 3 to distinguish DISH from AS. Since extraspinal ossifications may be more extensive than vertebral changes

(and may even exist without vertebral abnormalities), Utsinger *et al*. proposed another set of criteria in 1985; lowering the threshold for spinal involvement to two contiguous vertebral bodies in case peripheral enthesopathies were present.[225] The authors proposed that these criteria specifically could be used in epidemiological studies:

1. Continuous ossification along the anterolateral aspect of at least four contiguous vertebral bodies, primarily in the thoracolumbar spine. Ossification begins as a fine ribbon-like wave of bone but commonly develops into a broad, bumpy, buttress-like band of bone.
2. Continuous ossification along the anterolateral aspect of at least two contiguous vertebral bodies.
3. Symmetrical and peripheral enthesopathy involving the posterior heel, superior patella or olecranon, with the entheseal new bone having a well-defined cortical margin.

Probability of DISH was 'definite' if criterion 1 was present, 'probable' if criteria 2 and 3 were present and 'possible' if criterion 2 or 3 was present; particularly if calcaneal spurs occurred together with olecranon or patellar spurs. Exclusion criteria were: abnormal disc space height in the involved areas and/or apophyseal joint ankylosis.

Figure 2
Thoracic spine with 'flowing wax' ossification over more than four contiguous vertebrae with relative sparing of intervertebral disc height, typical for DISH.

The macroscopic criteria by which DISH is identified in paleopathological research have been slightly modified from the clinical radiographic criteria and consist of ossification of four contiguous vertebrae often limited to the right side in the thoracic spine in combination with extra-spinal manifestations such as new bone growth at insertions of entheses and ligaments.[181] In accordance with the Utsinger criteria Maat *et al*. proposed that in paleopathological studies the diagnosis DISH could also be established when ossification was present in less than four contiguous vertebral bodies 'if vertebral changes were supplemented by multiple peripheral enthesopathies (e.g. iliac whiskering, ischial wisping, patellar tufting, calcanear spurring)'.[123]

In spite of the efforts of the authors mentioned above, the criteria currently used may be of little use for clinical practice, since clinical symptoms may not correspond to the pathognomonic signs displayed on radiographs.[14] It was estimated that a period of approximately ten years is required for the pathologic process to evolve completely; making it extremely difficult to diagnose DISH (radiographically) in an early phase.[125] Furthermore, radiographs of the spine are seldom requested unless the patient has symptoms of back pain. To partly overcome this obstacle is was suggested that an anteroposterior chest radiograph is a reliable screening tool to diagnose DISH in the thoracic spine.[139] However, peripheral abnormalities may well exist without spinal involvement, yet at present there are no measures to establish that diagnosis.[128;225] In addition, the criteria suggested by Utsinger and Resnick have not been extensively investigated nor validated. The definition of DISH requires spinal involvement of four contiguous vertebrae; a number that was chosen purely arbitrarily. Therefore, it is important that new diagnostic criteria should be established and validated that (partly) incorporate clinical manifestations, distribution and features of peripheral joints and entheseal sites involved and radiological characteristics of regions other than the thoracic spine.[128] At present members of the Euro-DISH study group are exploring the possibility and reliability of such new diagnostic criteria (personal communication). Despite their clinical paucity, the criteria proposed by Resnick and Niyawama are still universally accepted and widely used in clinical literature and will also be used in this thesis (referred to as 'criteria of Resnick and Niyawama' or 'Resnick criteria').

Epidemiology

Studies investigating the epidemiology of DISH in Europe found prevalences ranging from 2.6% in females and 3.8% in males in the early 1980s in Finland to 15.1% in females in a recent Italian study.[96;167] In a Jewish hospital population over 40 years of age the prevalence of DISH was 22.4% in males and 13.4% in females.[18] In 1997 Weinfeld *et al*. studied a large population of hospitalized and outpatient individuals from two different hospitals in the USA and found a prevalence of 25% in males and 15% in females. They found lower prevalences of DISH among Afro-American, Native-American and Asian subpopulations, but these patient groups were relatively small.[234] Although ossification of

the posterior longitudinal ligament is not uncommon in the Japanese, DISH seems to be less prevalent in Asian populations; which was confirmed by the findings of Kim and coworkers, who described an overall prevalence of 2.9% in a large cohort of Koreans in 2004.[106;157] Extremely high prevalences of DISH have been described in Pima Indians, living in Arizona, USA; ranging from 25% and 4.7% in males and females aged 15 years and over, respectively, to 48% and 12% in males and females over the age of 55 years.[203] The Pima Indians have the highest reported prevalences of obesity and type 2 diabetes mellitus, which is hypothesized to result from an interaction between genetic predisposition and a sudden shift in lifestyle in the last century; from a traditional lifestyle characterized by a diet consisting of little animal fat and many complex carbohydrates and by great energy expenditure in physical labor, to a more sedentary lifestyle with the consumption of processed foods.[176] Since not all studies mentioned above used the formal Resnick criteria to diagnose DISH and different age groups were investigated, it is difficult to reliably compare the results. Additionally, no recent publications exist on the prevalence of DISH in a cross-sectional population in a Western European country, such as the Netherlands. The consistently encountered variation in prevalence among different human populations suggests, however, that genetic factors may well contribute to the development of DISH.

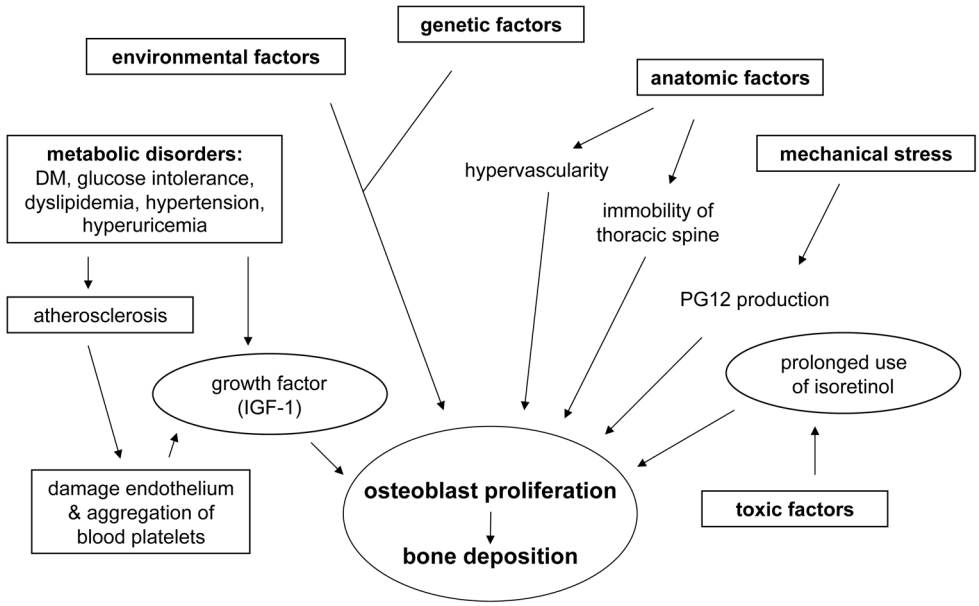

Figure 3
Possible pathogenetic mechanism driving bone deposition (adapted from Sarzi-Puttini).[188]

Etiology

The exact etiology of DISH is unknown, although genetic, metabolic, endocrinologic, anatomic, environmental and toxic factors have been suggested to play a role in the etiopathogenesis of the new bone formation in DISH (figure 3). Researchers seem to agree on two things with respect to the etiopathology of DISH: it is a disease of the elderly, as it is rarely seen before the age of 40 – 50 years, and it is more common in males than in females; with male:female ratio's varying from 2:1 to 7:1.[96;106] The association between obesity and DISH has been well known since the original description of Forestier and Rotes-Querol, where six out of nine patients were obese, and has been confirmed by several authors since.[97;108] In addition, DISH is suggested to be related to metabolic disorders such as hyperlipidemia and type 2 diabetes mellitus, but conflicting results on this topic have been published.[41;130;138] DISH seems to be highly associated with a lifestyle constituting of intake of large amounts of food without performing physical demanding work, as historically illustrated by the frequent findings of DISH in individuals of higher social status (e.g. monks, dukes) who were leading that lifestyle.[70;229] The prevalence of DISH is, therefore, likely to increase in the coming decades; not least as a result of global demographic ageing, but also because metabolic conditions associated with DISH, such as obesity and type 2 diabetes mellitus, have become endemic in modern-day Western societies.[202;240]

Other factors suggested to contribute to DISH include long-term treatment with synthetic vitamin A derivates, such as etretinate and isotretinoin, for acne and other skin disorders; which has been described to lead to DISH-like hyperostotic changes, particularly in the appendicular skeleton.[44;45] One pathological study found a significant increase in the number and width of nutrient foramina (indicating hypervascularity of the ossified ligaments and vertebrae involved) in addition to a significant increase in the size of the affected vertebrae, suggesting the possibility of a vascular etiology for this disorder.[51]
Forestier and Rotes-Querol described the flowing ossification in the thoracic spine to be grooved by the arteries originating from the aorta in their original report from 1950; suggesting that the presence of a (pulsating) vascular structure may inhibit new bone formation.[65] This hypothesis is supported by the fact that the ossifications in DISH are situated on the right side of the spine, *i.e.* contralateral of the aorta. The description of several patients with *situs viscerum inversus*, where the ossifications were located at the left side of the spine, is in line with this suggestion.[31;35] Apart from the descriptions of Forestier and coworkers there have been no (quantitative) reports on the morphology of the 'flowing wax' ossifications characteristic for DISH.

Clinical symptoms

Clinical symptoms of DISH are usually mild and develop slowly, even if radiological appearances can be dramatic. The spinal ossifications in DISH patients may lead to stiffness and a decreased range of motion of the spine, with or without associated pain in the middle to lower back.[14] Resnick and coworkers emphasized the extraspinal manifestations of DISH for the first time in their article from 1975; since then other authors reported osseous 'whiskering' at sites of ligament attachments in the pelvis (iliac crest, ischial tuberosity) and trochanters, calcanear 'spurs' at the attachments of the Achilles tendon and the plantar fascia as well as hyperostosis at the entheses of olecranon, patella, distal tibia and fibula. These ossifications can all be associated with vague, diffuse aching.[179] Enthesophytes (osseous outgrowths at the sites of attachment of tendon, ligament or capsule to bone) may affect virtually all joints.[132] The case-control study by Mata *et al*. reported patients with DISH to suffer more frequently from pain in the neck, thoracic spine, low back and extremities than controls, which was also associated with increased disability as assessed by health assessment questionnaires. On musculoskeletal examination DISH patients had greater reduction in neck rotation, thoracic movements and lumbar movement than healthy controls or patients with spondylosis deformans.[138]
In advanced stages of DISH, spinal ossifications may lead to complete ankylosis of the spine and postural changes typical for longstanding AS, such as forward stooping of the neck, high thoracic kyphosis and obliteration of the normal lumbar lordosis, have been described in DISH patients.[156]

Ossifications of the cervical spine may lead to pain and stiffness of the neck. Exuberant bony protrusions may cause complaints from adjacent soft tissue structures, resulting in hoarseness, stridor, sleep apnoea and dysphagia.[13;89;126;166] Clark referred to this process of difficulty in swallowing as 'DISHphagia' in 2003, which may result from mechanical compression and pressure, inflammation of tissues overlying spurs or pain combined with spasm of surrounding soft tissues.[36;52] More serious complaints from cervical ankylosis consist of myelopathy and cervical canal stenosis.[104;205] The combination of ligamentum flavum ossifications and hyperostosis of the posterior spinal elements may lead to symptomatic spinal canal stenosis in the lumbar spine as well. Significant compression of the inferior vena cava caused by large anterior lumbar excressences has incidentally been reported.[190]

Little has been published about the pharmacologic and nonpharmalogic management of DISH patients, who may complain of pain and decreased mobility of virtually all joints. Simple analgesics or non steroid anti-inflammatory drugs (NSAIDs) may be helpful for spinal en peripheral complaints.[14] Some articles reported physiotherapy, chiropractic manipulation or even acupuncture to be beneficial, but the efficiency of these modalities has not been proven.[3;146]
Surgical intervention may be necessary in some cases, for example, resection of the bony outgrowths in the cervical spine may be beneficial in selected cases where exuberant

cervical ossifications cause dysphagia or airway obstruction.[224] When spinal canal stenosis in the lumbar spine leads to (progressive) myelopathy decompressive laminectomy combined with posterior stabilization may be performed.[102;118] Perioperative challenges that can be expected in DISH patients consist of intubation difficulty and respiratory distress in the early postoperative period due to cervical osteophytes.[71;126] Extensive heterotopic ossification after hip arthroplasty has also been described in DISH patients.[23]

Spinal fractures in the ankylosed spine

To spine surgeons the most interesting and clinically relevant aspect of the ankylosed spine may be the increased risk for spinal fractures that results from a completely stiff spine. This feature is well known in patients with advanced AS; some authors suggested patients with AS to have a four- to eightfold fracture risk during their lifetime compared to unaffected individuals.[59;244] With increasing frequency, however, cases are being reported of DISH patients with unstable spinal fractures, often associated with neurological deficits, after relatively minor trauma; comparable to AS patients.[49;90] AS is an inflammatory disorder associated with the HLA-B27 gene, in which chronic inflammation of the sacroiliac joints and the spine eventually leads to complete ankylosis of the spine. It affects males more frequently and its prevalence is stable around 0.1 – 1.4%.[21] It typically starts in adolescence and may lead to considerable morbidity and disability in advanced stages.[9;230] After a

Figure 4
CT scan of a fracture in an ankylosed thoracic spine due to DISH.

substantial disease duration complete spinal ankylosis in combination with vertebral osteoporosis may lead to spinal fractures, even after minor trauma. A spinal fracture, with subsequent neurologic deficit as a result from unstable fracture configuration, is a well known and feared complication of AS.[151] Although in end stage DISH complete ankylosis of the spine may also occur, there is still little awareness for spinal fractures after trivial trauma in DISH patients (figure 4).[128;197]

The diagnosis of fracture is often delayed in DISH, since patients frequently have baseline spinal complaints that may not easily be distinguished from fracture pain by both patients and doctors. Physicians may not consider the probability of a spinal fracture in patients with DISH, as these fractures often result of trivial trauma. Furthermore, low awareness for the disorder and its potential dangers leads to underdiagnosis. Finally, spinal radiographs of patients with DISH may be difficult to interpret due to pre-existing pathological changes, which may mask (minimally displaced) fractures.[80] Because of intrinsic unstable fracture configurations, high rates of primary and secondary neurological consequences have been described in DISH patients.[29;88] Although solid data on clinical outcome of patients with ankylosing spinal disorders (ASD) such as DISH and AS are absent, many retrospective case reports and small series indicate that patients with ASD with a spinal fracture have an increased risk for neurological deficit, morbidity and mortality.

Some authors previously suggested that pattern of injury in patients with multilevel spinal ankylosis is different compared to patients with unrestricted spinal motion.[40;73] In patients with normal range of motion in the spine, hyperextension injuries are rarely reported other than in the cervical spine; in the thoracolumbar spine they represent less than 3% of all fractures in large series and are usually the consequence of high energy injuries.[24;133] In patients with ASD, however, hyperextension fracture-dislocations of the thoracolumbar spine are not at all unusual.[20;25;81;145] Loss of compensatory motion of the IVD and facet joints in the affected area may contribute to this fracture pattern. Multilevel ankylosis leads to long lever arms that concentrate stress and deformation at the site of the injury and does not allow for dispensation of energy. In case the ankylosed spine is exposed to hyperextension forces, due to a simple backward fall or low velocity rear impact motor vehicle accident for instance, the anterior column is at risk for failure under tension and the anterior longitudinal ligament and other surrounding soft tissues may be disrupted, leading to unstable fractures.[25]

Although AS and DISH both lead to complete ankylosis of the spinal column, they are different pathophysiological entities. They constitute different biomechanical configurations with distinct modes of failure, reflected in the predilection place for fractures within the IVD in AS, while fractures in DISH are reported to be more frequently localized in the vertebral body.[88] In AS, ossification starts within the peripheral layers of the annulus fibrosis, forming thin and slender vertically orientated syndesmophytes bridging adjacent vertebrae. Chondroid metaplasia and gradual calcification of the annulus fibrosis and

nucleus pulposus lead to a functional degradation of the IVD making it the weakest link in the AS affected spine. After longstanding disease, however, the entire disc may ossify which in combination with increased vertebral osteoporosis makes the vertebral body weaker than the adjacent disc space. This may explain why fractures in AS occur predominantly in the IVD space early in the disease and through the vertebral body in advanced stages of AS.[164] DISH produces more exuberant new bone formations, reaching up to 20 mm thickness, orientated anterolaterally from the spine.[64;177] The ankylosing bridges are often thickest and strongest at the level of the IVD. This phenomenon, combined with relative preservation of the strong tissue of the annulus fibrosis, may explain why fractures develop less easily at the level of the IVD than through the vertebral body where ligament ossification is minimal.[88] However, not all authors agree on the predilection for fractures through the vertebral body in DISH.[80]

Bone mineral density in DISH

The definition of DISH and the frequently used term *ossifying diathesis* suggests a generalized state of increased bone formation. In addition, the exuberant ossifications on the anterolateral aspect of the thoracic spine as seen on chest radiographs may lead to an impression of skeletal robustness, which seems to contradict the reported increased fracture risk in DISH patients. In accordance with the impression of hyperostosis, bone mineral density (BMD) of patients with DISH has been demonstrated to be increased compared to control individuals, using different methods for measuring BMD in different parts of the skeleton.[43;76] Sahin *et al.* suggested the fracture risk to be decreased in patients with DISH because of higher BMDs.[186] BMD measurements of the spine may not be reliable in DISH patients, however, since measurements may be influenced by the ossifications in the DISH affected spine. The example presented by Schwartz *et al.* reports a case of an elderly man who was found to have a bone density in the lumbar spine above the upper expected value for a young individual, while the measurement of the forearm revealed an osteoporotic bone status. When conventional radiographs of the lumbar spine were ordered they demonstrated abundant flowing ossifications consistent with DISH. The authors suggested, therefore, that the increased (incorrect) BMD measurement was caused by the ossifications of DISH in the field of view.[195] In can be hypothesized that the ossifications may project in the scanning field and artificially elevate BMD measurements in DISH patients, while the *vertebral* BMD may be comparable or even decreased in DISH; masking pre-existing osteoporosis for example.

Objectives of this thesis

The main objective of this thesis was to investigate whether DISH represents a clinical important systemic disorder with potential morbidity or, as suggested by some authors, a harmless radiographic curiosity. Particular emphasis was placed on the current prevalence of DISH in the Netherlands, the clinical outcome of patients with DISH after a spinal fracture and the distinctive morphology of the spinal ossifications with respect to fracture characteristics specific for DISH. The studies presented in this thesis were guided by the following research questions:

- What can be learned from previously published articles about the clinical outcome of patients with ankylosing spinal disorders with traumatic spinal fractures?
- What is the current prevalence of DISH in the Netherlands and what trends can be expected for the future?
- What can be learned about the morphology of the spinal ossifications in DISH and do characteristics of this morphology explain fracture patterns in DISH?
- Is the morphology of the spinal ossifications in DISH influenced by the presence of a vascular structure?
- Is the bone mineral density of the spine in DISH different than in controls?
- Is the clinical outcome after a traumatic spine fracture different for patients with ankylosing spinal disorders compared to control patients?

Contents of this thesis

An increasing amount of evidence suggests that patients with DISH are at risk for unstable spinal fractures of the spine following minor trauma, comparable to the fracture mechanism in AS patients. By pooling data from previously published papers, we aimed to increase knowledge on the clinical outcome of patients with ankylosing spinal disorders with spinal fractures. In **chapter 2** a systematic review of the literature published between 1980 and 2007 is presented in which treatment strategies, neurological status and complications in patients with AS and DISH after spinal injury were evaluated.
To get insight in the current proportion of individuals with DISH in the Netherlands the prevalence of DISH in an outpatient population over 50 years of age was studied. We reviewed the chest radiographs of patients, visiting the outpatient clinic of the Department of Internal Medicine for a first consultation, and recorded the number of patients showing distinct radiographic features of DISH. In order to predict possible future trends in the prevalence of DISH, the relationship between age, gender and the presence of DISH was investigated as well. The results of this study are presented in **chapter 3**.
The presence of exuberant ossifications on conventional radiographs can give the impression of skeletal robustness in DISH patients; however, the increased fracture risk proposed in this patient category suggests the opposite. The seemingly contradictory relation between increased bone formation in DISH on the one hand and elevated fracture

risk on the other will be explored in **chapter 4 and 5**. Since fractures in spines with DISH are reported to more frequently occur at the level of the vertebral body, as opposed to AS spines where fractures usually occur at the level of the IVD, we examined the exact morphology of the 'flowing wax' ossifications in DISH; in order to better understand the configuration of the bony outgrowths with respect to fracture biomechanics. In **chapter 4** we studied the exact spatial characteristics of the ossifications by calculating the transverse area and centroid (geometric center) of the ossifications in cadaveric spines with DISH on CT scans. In addition, we investigated whether the morphology of the ossifications may be influenced by the presence or absence of a vascular structure. With the use of computed tomography angiography (CTA) scans of patients with DISH, the localizations of the vertebral segmental arteries (VSAs) in relation to the ossifications were reviewed and compared to unaffected control patients.

In accordance with the impression of skeletal robustness due to increased bone formation, some authors previously suggested the BMD of patients with DISH to be increased compared to controls, yet the previously mentioned fracture risk in DISH patients contradicts great skeletal strength. We were interested to see to what extend BMD measurements in patients with DISH may be influenced by the spinal ossifications, since the presence of the ossifications in the scanning field may lead to unreliable BMD measurements. In **chapter 5** we quantitatively investigated the exact contribution of the spinal ossifications on BMD measurements by calculating BMDs from different experimental orientations in cadaveric spines with DISH and comparing the results to measurements in unaffected control spines.

Finally, we investigated the clinical outcome of patients with DISH and AS treated for traumatic spinal fractures in our own institution between 2003 and 2009 in **chapter 6**. Since the results of the literature review suggested that the clinical outcome after a traumatic spinal fracture may be highly influenced by the presence of ASD, this retrospective review focused on mortality, neurological function and complications of patients with ASD, compared to control patients.

In **chapter 7** a proposition of future directions on the research on DISH will be given and some clinical considerations will be provided. The final chapter, **chapter 8**, presents the summary and conclusions of this thesis.

CHAPTER 2

Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications

LA Westerveld
JJ Verlaan
FC Öner

Eur Spine J 2009;18(2):145 – 56

Abstract

Background

The ankylosed spine is prone to fracture after minor trauma due to its changed biomechanical properties. Although many case reports and small series have been published on patients with ankylosing spondylitis (AS) suffering spine fractures, solid data on clinical outcome are rare. In advanced diffuse idiopathic skeletal hyperostosis (DISH), ossification of spinal ligaments also leads to ankylosis. The prevalence of AS is stable, but DISH may become more widespread due to its association with age, obesity and type 2 diabetes mellitus.

Methods

A systematic review of the literature was conducted to increase knowledge on treatment, neurological status and complications of patients with preexisting ankylosed spines sustaining spinal trauma. A literature search was performed to obtain all relevant articles concerning the outcome of patients with AS or DISH admitted with spinal fractures. Predefined parameters were extracted from the papers and pooled to study the effect of treatment on neurological status and complications.

Results

Ninety-three articles were included, representing 345 AS patients and 55 DISH patients. Most fractures were localized in the cervical spine and resulted from low energy impact. Delayed diagnosis often occurred due to patient and doctor related factors. On admission 67.2% of the AS patients and 40.0% of the DISH patients demonstrated neurologic deficits, while secondary neurological deterioration occurred frequently. Surgical or conservative treatment did not alter the neurological prospective for most patients. The complication rate was 51.1% in AS patients and 32.7% in DISH patients. The overall mortality within three months after injury was 17.7% in AS and 20.0% in DISH.

Conclusions

This review suggests that the clinical outcome of patients with fractures in previously ankylosed spines due to AS or DISH, is considerably worse compared to the general trauma population. Considering the potential increase in prevalence of DISH cases, this condition may render a new challenge for physicians treating spinal injuries.

Introduction

The ankylosed spine is prone to fracture even after trivial trauma.[91] Several authors have shown patients with ankylosing spondylitis (AS) to have a fourfold fracture risk during their lifetime compared to unaffected individuals.[59;244] In AS spontaneous fusion of the sacroiliac joints and spine occurs due to chronic inflammation leading to initial back pain followed by generalized stiffness of the spine. The disease has a prevalence of 0.1 – 1.4%; typically affects males and usually becomes apparent between 20 and 30 years of age.[21] Due to multilevel bony fusion, long lever arms develop in the spinal column on which forces can act during trauma.[49;155] During progression of the disease the spine becomes increasingly susceptible to injury, eventually even after low energy impacts.[22;90;211] Fractures in the ankylosed spine are often unstable due to the ossification of supportive and elastic soft tissues and may cause neurologic deficit as a result of dislocation.[116;209] Moreover, because of unstable fracture configurations, initially intact patients may sustain secondary neurologic deterioration after unprotected transfers and manipulation.48 Neurological deficit after fracture is a well known and feared complication in AS, therefore these patients should be handled with great care when a fracture is suspected.[151;173]

Diffuse idiopathic skeletal hyperostosis (DISH) is a supposedly non-inflammatory disease in which spinal longitudinal ligaments and entheses slowly become ossified leading to decreased mobility of the affected region until complete ankylosis follows.[14] DISH is diagnosed when flowing ossification of the anterior longitudinal ligament is present on spine radiographs over at least four consecutive levels.[179] Its etiology is unknown, but associations with obesity, type 2 diabetes mellitus and advanced age have been demonstrated by several authors.[41;108] Studies investigating the demographic characteristics of DISH have found a prevalence ranging from 2.9% in a Korean population to 25% in a selected population of Caucasian males in the United States of America.[106;234] Acknowledging that DISH is associated with traits typical of modern affluent societies such as increasing life expectancy, obesity and type 2 diabetes, its prevalence and degree of expression can be expected to increase during the coming decades.[202;240] Most symptoms of DISH are mild and develop slowly but an increasing amount of evidence suggests that DISH is a less innocent condition than previously assumed.197 Serious complications of DISH in the cervical region for example, are dysphagia, difficult endotracheal intubation, myelopathy and spinal canal stenosis.[168;205] Some authors have speculated that patients with DISH are also at risk for spinal fractures after minor impacts, comparable to the fracture mechanism of AS patients.[14;164]

This systematic review aims to increase the knowledge on treatment, neurological status and complications of trauma patients with ankylosed spines (due to AS or DISH) and admitted with spine fractures, by pooling data previously published in the literature.

Methods

To identify the relevant publications on this subject, a Medline and EMBASE search was performed. References were obtained from the search parameters 'ankylosing spondylitis' AND 'trauma' and 'diffuse idiopathic skeletal hyperostosis' AND 'trauma' (and their respective synonyms). Articles in languages other than English, French or German and articles without abstract were excluded. All articles were initially screened for relevance by title and abstract. Inclusion criteria were: publication date between January 1st 1980 and December 31st 2007, the presence of AS or DISH and a spinal fracture, a sufficiently detailed description of fracture type and trauma mechanism, an adequate description of neurological status, complications and period of follow up.[7] The first three months after admission were (arbitrarily) defined as the post treatment phase; thereafter it was defined as the follow up phase. Consequently, patient's data were only included in the follow up group if this period (≥ 3 months) was specifically described in the article. If not, data were only included for the post treatment phase. Sufficiently described case reports were included to obtain as much information as possible on this subject, simultaneously acknowledging the limited number of large-scale case series expected to be available in the literature. A cross-reference search was performed to obtain the remaining articles. Two authors performed the close reading of all papers and extracted data independently to minimize selection bias and errors. The parameters obtained from the papers and their definitions are listed in table 1. The data from both readers were compared and where they differed, the pertaining paper was reread until consensus was reached. If overlap was present in two papers from the same author or institution, the least informative paper was excluded. The level of evidence of the included articles was determined according to the guidelines proposed by the Center for Evidence Based Medicine (CEBM).[161] The independent samples t test was used to determine statistical significance between the AS and DISH groups (SPSS version 12.0.2; SPSS Inc., Chicago, USA).

Results

The literature search and cross-referencing resulted in a total of 1,035 references (951 on AS and 84 on DISH) of which 894 were rejected due to off topic abstract content and/or failure to meet the inclusion criteria. After reading the remaining 141 full text papers (109 on AS and 32 on DISH), another 48 were excluded because of insufficient detail, overlap of same author/institution or uncertain history of trauma. The remaining 93 articles were included:

- Ankylosing spondylitis: 76 articles, describing a total of 345 patients. [2;5;12;20;22;34;38;42;49;50;53-55;59-61;63;66-68;72;73;75;77;78;81-83;90;93;99;101;103;105;109;115;116;121;122;136;141-143;147;149;151;155;162;165;170-173;182;185;187;189;191;194;198;199;206;209;211;212;215-219;221;223;232;233;237;243]
- Diffuse idiopathic skeletal hyperostosis: 17 articles, describing a total of 55 patients.[15;25;29;37;58;62;88;95;117;137;145;148;164;204;207;237;242]

All papers described retrospective case series or case reports, therefore all were assigned grade 4 level of evidence.

Table 1
Parameters extracted from the papers.

Parameter	Definition
Name and affiliation of the authors	
Year of publication and name of journal	
Study design	Prospective, retrospective, case report (n = 1 or n = 2), case study (n ≥ 3 individuals)
Follow up	Months
Quality of paper	Oxford Center for Evidence-based Medicine, levels of evidence[161]
Mean age of patients	Years
Male/total ratio	Number of males divided by the total number of patients
Traumatic impact	High: motor vehicle accident, fall > 15 feet[6] Low: fall from standing or sitting position
Polytrauma patients (%)	Number of polytrauma patients reported divided by the total number of patients reported
Fracture level	Cervical, thoracic, lumbar, sacral
Fracture type	Hyperextension, flexion, compression, rotation
Type of treatment	Surgical: posterior fixation, anterior fixation, combined anterior-posterior fixation, laminectomy Conservative: halo traction, halo immobilization, collar, brace, plaster jacket, bed rest
Immobilization type	Halo traction, halo immobilization, collar, brace, plaster jacket, bed rest, none
Immobilization duration	Weeks
Neurological outcome	ASIA Impairment Scale[7]
Complications	Neurologic deterioration, deep venous thrombosis, pulmonary embolism, wound infection, cystitis, pneumonia, pseudoarthrosis, decubitus, miscellaneous complications
Delayed diagnosis	Diagnosis established > 24 *h* after trauma
Mortality	Number of deceased patients

Table 2
Patient characteristics.

	AS	DISH	p-value
Number of articles	76	17	
Mean follow up (range)	11.2 (1 – 65)	12.0 (1 – 32)	0.851
Number of patients	345	55	
Mean age (range)	59.1 ± 12.6 (32 – 82)	68.2 ± 10.2 (44 – 82)	0.004
Gender ratio	0.90	0.84	0.538
Polytrauma patients	1.4%	10.9%	0.034

General information on the study population

The mean patient age was 59.1 years for AS and 68.2 years for DISH; the difference between the mean age of both groups was statistically significant (p = 0.004). Both groups consisted predominantly of males (male/total ratio was 0.90 in AS; 0.84 in DISH). The mean duration of follow up was 11.2 months for AS and 12.0 months for DISH. Male/total ratio and follow up duration were comparable in the AS and DISH groups (p > 0.05). The percentage of DISH patients with multiple trauma significantly exceeded AS patients; 10.9% in DISH *vs.* 1.4% in AS (p = 0.034). In table 2 details on the characteristics of the study population are presented.

Trauma mechanism, fracture location and diagnosis

The majority of patients sustained low energy trauma causing their fracture; 227 patients with AS (65.8%) and 38 patients (69.1%) with DISH had low energy impacts. In most cases the trauma mechanism consisted of a fall from standing/sitting position. High energy impacts caused a fracture in 107 patients with AS (31.0%) and 13 patients with DISH (23.6%). In 11 patients with AS and four patients with DISH there was no recollection of trauma at all.

Most fractures were localized in the cervical spine; this was the case for 280 AS patients (81.2%) and 33 DISH patients (60.0%). Fractures of the thoracic spine were described more often in patients with DISH (34.5%) than in AS (10.7%). Fractures of the lumbar spine occurred in 27 AS patients (7.8%) and three DISH patients (5.5%). One sacral fracture occurred in a patient with AS. Hyperextension was the most frequent cause of fracture, representing the trauma mechanism for 96 patients with AS (74.4% of 129

Table 3
Fracture type *vs.* fracture level in patients with AS (based on 129 patients).

	Cervical	Thoracic	Lumbar	Sacral	Total
Extension	68 (68.0%)	15 (93.7%)	12 (100%)	1 (100%)	96 (74.4%)
Flexion	20 (20.0%)	0	0	0	20 (15.5%)
Compression	5 (5.0%)	1 (6.3%)	0	0	6 (4.7%)
Rotation	7 (7.0%)	0	0	0	7 (5.4%)
Total	**100**	**16**	**12**	**1**	**129 (100%)**

Table 4
Fracture type *vs.* fracture level in patients with DISH (based on 43 patients).

	Cervical	Thoracic	Lumbar	Total
Extension	12 (44.4%)	10 (71.4%)	0	22 (51.2%)
Flexion	0	0	0	0
Compression	3 (11.1%)	2 (14.3%)	1 (50%)	6 (14.0%)
Rotation	12 (44.4%)	2 (14.3%)	1 (50%)	15 (34.9%)
Total	**27**	**14**	**2**	**43 (100%)**

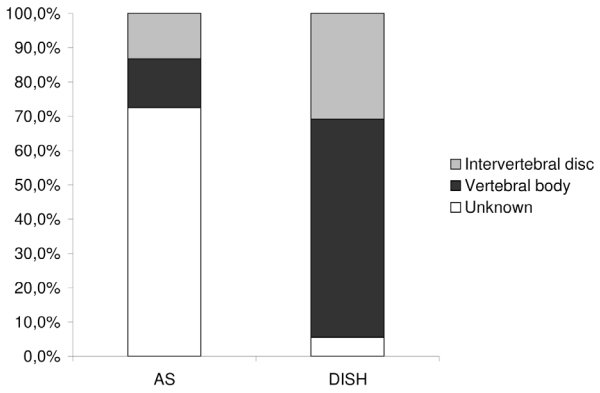

Figure 1
Fracture localization in vertebral body or intervertebral disc (based on 345 AS and 55 DISH patients).

reported cases) and 22 patients with DISH (51.2% of 43 reported cases). Flexion-type fractures occurred in 20 AS patients (15.5%) and in none of the DISH patients. Compression fractures were described in six AS patients and in six DISH patients. Rotation-type fractures were reported in seven patients with AS *vs.* 15 patients with DISH. Details of the fracture type in relation to fracture level are listed in tables 3 and 4.
In patients with DISH the majority of fractures observed were through the vertebral body (63.6% of the total number of fractures), whereas in AS patients, the number of fractures through the vertebral body equaled the number of fractures through the IVD (see also figure 1). The large difference in number of fracture patterns reported for AS and DISH unfortunately prevents any quantitative comparison.
A delay in diagnosis often occurred; in 59 patients with AS (17.1% of the total AS population) the fracture was not diagnosed within 24 hours following trauma. In 31 patients (52.5% of these 59 patients) the fracture was not timely recognized by the physician ('doctor's delay'), while 28 patients (47.6%) delayed their decision to seek medical attention ('patient's delay'). In five patients with DISH (9.1%) the diagnosis was delayed by failure to identify the fracture, thus representing 100% doctor's delay.

Treatment

Surgical treatment was performed in 187 AS patients (54.2%) and in 30 DISH patients (54.5%) and consisted mainly of posterior fixation. In AS patients posterior procedures were more often combined with decompression of the spinal cord than in patients with DISH. In most articles the rationale behind the treatment strategy was not described, but reasons reported often were: (secondary) deterioration of neurological status, unstable fracture configuration and the presence of an epidural hematoma. Conservative treatment was performed in 158 AS patients (45.8%) and 25 DISH patients (45.5%) respectively. The main reason to refrain from surgery was high surgical risk or patient refusal.

In conservative treatment patients with DISH were most frequently treated with a collar whereas patients with AS were predominantly treated with cervical traction or collar. Immobilization by braces was applied in 16.0% of the DISH patients *vs*. 3.8% of the AS patients, possibly reflecting the larger number of thoracic fractures for DISH patients (figures 2 and 3).

Neurological status

At the time of admission 232 AS patients (67.2%) had a neurologic deficit (ASIA A-D) *vs*. 22 DISH patients (40.0%). Secondary deterioration of neurological status was observed in 48 patients AS patients (13.9%) and in eight DISH patients (14.5%) in the post treatment phase (< 3 months). In the follow up phase (> 3 months) three AS patients and one DISH patient showed neurological deterioration. In the majority of cases the definitive treatment (whether surgical or nonoperative) did not influence the outcome of neurological status. In the surgical group 111 AS patients (59.4%) showed no change in neurological function within the first three months, *vs*. 23 DISH patients (76.7%).

At follow up the majority of patients had the same degree of neurological deficit they had in the post treatment phase; 77 AS patients (73.3%) and 20 DISH patients (90.9%), respectively. Improvement of neurological status was described in 51 AS patients (27.3%) and two DISH patients (6.7%) in the post treatment phase and in 28 AS patients (26.7%) and in two DISH patients (9.1%) at follow up. In the conservatively treated patients 126 AS patients (79.7%) and 21 DISH patients (84.0%) demonstrated no change in neurological function during the post treatment phase, at follow up this was the case in 79 AS patients (74.5%) and 15 DISH patients (88.2%). In nine AS patients (5.7%) and one DISH (4.0%) patient neurological status improved in the post treatment phase; at follow up 24 AS patients (22.6%) and one DISH patient (5.9%) showed improvement of neurological

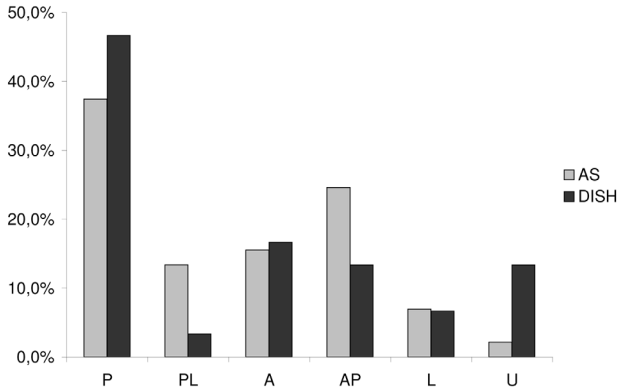

Figure 2
Surgical treatment in 345 AS and 55 DISH patients. **P** posterior fixation, **PL** posterior fixation combined with laminectomy, **A** anterior fixation, **AP** combined anterior-posterior fixation, **L** laminectomy, **U** unknown.

function. Overall, surgical treatment seemed to lead to neurological improvement in more AS and DISH patients than conservative treatment; both in the post treatment phase and at follow up. Most patients improved one ASIA scale; this was the case in 36 patients with AS and three patients with DISH. A total of 13 AS patients improved two scales, nine patients improved three scales and in two patients an improvement of four ASIA scales was reported. In DISH patients improvements of only one ASIA scale were observed (see also tables 5 and 6).

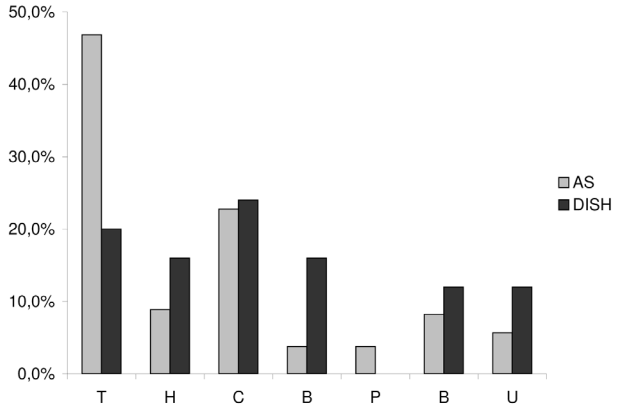

Figure 3
Conservative treatment 345 AS and 55 DISH patients**. T** halo traction, **H** halo immobilization, **C** collar, **B** brace, **P** plaster jacket, **B** bed rest, **U** unknown.

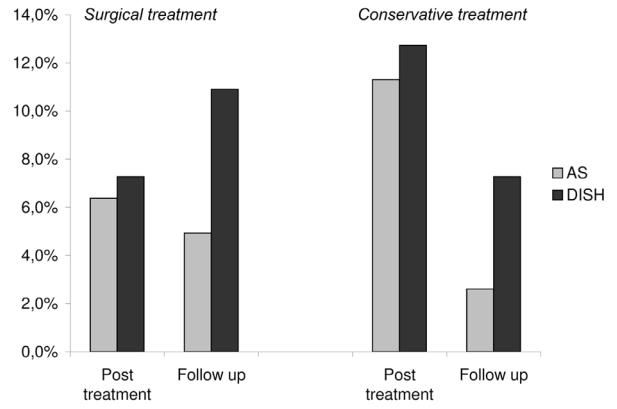

Figure 4
Mortality in 345 AS patients and 55 DISH patients.

Table 5
Neurological status in 345 patients with AS.

Surgical treatment

Post treatment	N/K	A	B	C	D	E
N/K*		1				
A		28	3	1	5	2
B			6	4	7	4
C			1	8	5	5
D		1	2	3	23	15
E		7	1	7	3	45

Conservative treatment

Post treatment	N/K	A	B	C	D	E
N/K	1					
A		47				
B			8			
C		4		10	1	
D		2		2	27	8
E		9	1	2	3	33

Follow up	A	B	C	D	E
A	17				1
B		2		5	
C			5	8	2
D				16	12
E					37

Follow up	A	B	C	D	E
A	26	1	2	1	1
B		1	1	3	
C			1	8	
D			1	18	7
E	1			1	33

* N/K = not known. Patients admitted with EMV = 3; therefore ASIA classification could not be assessed

Table 6
Neurological status in 55 patients with DISH.

Surgical treatment

Post treatment	A	B	C	D	E
A	5	1			
B					
C			3	1	
D	1			4	
E	1			3	11

Conservative treatment

Post treatment	A	B	C	D	E
A	5				
B					
C				1	
D				1	
E	2			1	15

Follow up	A	B	C	D	E
A	6				
B		1			
C			2	1	
D				3	1
E					8

Follow up	A	B	C	D	E
A	1				
B					
C					
D				1	1
E	1				13

Bold values in table 5 and 6 stand for the number of patients in which neurological status (presented in ASIA grades) was unchanged after treatment (A – A, B – B, C – C etc).

Complications

In seven patients with AS, uncommon complications of spinal fractures were described, such as aortic dissection (four patients)[55;189;191;219], aortic pseudoaneurysm (one patient)[122] and tracheal rupture (one patients).[105] Most of these complications were lethal (in four patients).

Besides these uncommon findings, general complications such as postoperative wound infections, deep venous thrombosis, pneumonia and respiratory insufficiency were frequently reported complications in both AS and DISH patients; the latter two complications were common and led to fatal outcome in many cases. In some articles complications (whether fatal or not) may not have been fully reported. Based on the data provided, however, the complication and mortality rate seemed to be higher in conservatively treated patients than in surgically treated patients (see table 7 for details).

Mortality

The overall mortality in the post treatment phase was comparable in both study groups; 6.4% in AS *vs*. 7.3% in DISH in the surgically treated patients and 11.3% in AS *vs*. 12.7% in DISH in the nonoperatively treated group. At follow up the mortality in the surgically treated group was 4.9% for patients with AS and 10.9% for patients with DISH. The mortality in nonoperatively treated patients with DISH was also higher than in AS at follow up; 7.3% *vs*. 2.6%, respectively.

These differences were not statistically significant (see also figure 4). A small number of AS patients died in the acute phase after trauma or intraoperatively as a result of severe complications such as lacerations of the aorta or trachea (see complications).

The most frequent cause of death for both study groups, however, was pneumonia and/or respiratory failure; both in the post treatment phase and at follow up. The cause of death was not reported in 21 AS patients and in 13 patients with DISH.

Table 7
Complications in patients with AS and DISH: number of patients reported (fatal outcome).

	AS		DISH	
Complication	**ST**	**CT**	**ST**	**CT**
Aortic dissection	3 (2)	1 (1)		
Aortic pseudoaneurysm	1			
Cervical myelopathy		1 (1)		
Cardiac arrest	1 (1)	4 (4)		1 (1)
Cerebrovascular accident	4 (3)			
Decubitus	1	2		
Deep venous thrombosis	2			1
Epidural hematoma	7	4	1	
Epilepsy		1 (1)		
Esophago-cutaneus fistula from tracheotomy		1		
Gastrointestinal tract bleeding	1	6		
Hemothorax	1	1	1	1
Heterotopic ossification		1		
Instrumentation failure	33	3	1	
Massive hemorrhage during surgery	3			
Multiple organ failure				1 (1)
Nonunion/pseudoarthrosis		6		
Pneumonia	12 (10)	22 (18)	2	3 (2)
Pulmonary embolus	3 (3)	2 (2)		
Respiratory insufficiency	10 (6)	24 (10)		5 (4)
Sepsis	2 (1)	2 (2)		
Tracheal rupture		1 (1)		
Wound infection	9	1	1	
Total number reported (fatal outcome)	**93 (26)**	**83 (40)**	**6**	**12 (8)**
% total reported (% fatal outcome)	**27.0 (7.5)**	**24.1 (11.6)**	**10.9**	**21.8 (14.5)**

ST surgical treatment, **CT** conservative treatment

Discussion

In the present study a systematic review of the literature was performed to increase the knowledge of treatment, neurological status and complications of patients with an ankylosed spine, due to AS or DISH, sustaining spinal fracture. The study groups were comparable with respect to gender ratio and follow up duration. The mean age and the number of polytrauma patients were significantly higher in the DISH group than in the AS group. This renders in the authors' opinion direct quantitative comparison of the treatment strategies, neurological outcome and complications of both groups impossible. Regarding the limited number of papers available, the weak study designs and low level of evidence of all articles, it follows that evidence is rather limited (immediately uncovering a weakness of the present study since it is based on these papers). The absence of adequate follow up data can be considered the most significant weakness of the majority of papers included and may reflect the remarkably high morbidity/mortality rates of trauma patients with ankylosed spines compared to a 'regular' trauma population. From studies conducted previously to establish the outcome of traumatic spine fracture treatment, it was concluded that sufficient long term follow up has invariably been difficult to establish in these cohorts of patients.[69;111]

Some findings of the present study, however, deserve special attention. The majority of fractures was caused by low energy impacts and was localized in the cervical spine. The cervical region is the most vulnerable part of the spinal column because of increased mobility, small vertebral bodies, oblique articular facets and the mobility of the heavy skull on the cervical spine.[196;238] Mac Millan *et al*. stated that traumatic fractures in patients with a partially fused spine tend to occur adjacent to the fused segments, rather than through the fused region itself.[124] Paley *et al*. also reported fractures to occur at the junction of the mobile and the fused spine.[164] Hendrix *et al*. found an association between the number of contiguously ankylosed segments of the spine and increased fracture instability.[80] It can be hypothesized that the biomechanically vulnerable cervicothoracic junction becomes even more susceptible to injury in case of ankylosis since forces can act on longer lever arms.

In patients with AS, both doctor's delay and patient's delay in diagnosis occurred. Patient's delay may have been caused by preexisting back pain not instantly distinguishable from fracture pain. Indeed, in some cases AS patients did not notice any symptoms as a result of fracture until abrupt neurological deterioration occurred.[194;223] This phenomenon is referred to as 'the fatal pause' because of the delayed development of neurological deficits.[48] The absence of major trauma in the patient's history may also lead to doctor's delay, since spinal fractures will be suspected less after a trivial fall. Furthermore, radiographs of patients with ankylosing spine disorders may be difficult to interpret, due to preexisting pathologic osseous changes.[80] In DISH patients all delayed diagnoses were caused by doctor's delay, possibly because of low awareness for this condition. This low awareness may also be responsible for the limited number of cases reported in the literature.

In patients with DISH the fracture was more often through the vertebral body than through the IVD. Some authors have previously suggested that the fracture mechanism may be different for AS and DISH, since AS fractures tend to occur more often at the level of the IVD while DISH fractures tend to occur at the level of the vertebral body.[73]

A functional degradation of the IVD because of chondroid metaplasia and loss of elasticity due to calcification of the annulus fibrosis and nucleus pulposus making the IVD the weakest link in the AS affected spine, may contribute to this level dependent fracture configuration.[164] In advanced stages of DISH exuberant bone/calcifications are formed in the anterior longitudinal ligament, especially at the level of the IVD. It is suggested that at this level fractures may develop less easily than through the vertebral body where ligament ossification is minimal. Stress shielding as a result of load transfer through ossified ligaments leading to weakening of the vertebral body may also play a role in DISH fracture initiation and propagation.[19] Unfortunately, fracture patterns were only described in 95 AS patients (27.5% of the total AS group) so no solid conclusions could be drawn on this interesting subject.

The number of patients suffering from a neurological deficit was high in both groups; many patients with AS and DISH were admitted with a degree of neurological deficit. Worsening of neurological function due to inadequate immobilization, inconsiderate transfers or application of a hard collar on the cervical spine with pre-existing kyphotic deformity was reported in several articles.[122;137;165;223] Compared to studies describing (healthy and considerably younger) individuals sustaining traumatic spine fractures where only 0.08% of the patients deteriorated in neurological function, these numbers are of major concern.[228] It is suggested that patients with traumatic fractures of the ankylosed spine are not only susceptible to initial neurological deficit but also to secondary neurological deterioration due to highly unstable fracture configurations between the fused segments.[22] In the absence of a definite stabilization method, transfer and manipulation of these patients should proceed with utmost care.

Different types of complications were reported for patients with AS and DISH. In some articles concerning AS patients, rare complications such as aorta laceration and rupture of the trachea were described. Aortitis is a known complication of AS, in which adventitial scarring, intimal proliferation and fibrous thickening of the aortic wall are commonly seen.55;226 Thoracic and lumbar injuries in AS patients may be associated with injury to the aorta either due to direct mechanical trauma or to blunt forces associated with the spinal fracture.189 However, laceration may be most likely the result of pathophysiological changes that cause the aorta to become firmly adherent to the anterior longitudinal ligament and subject this structure to shearing forces during fracture dislocation.[55;191]

The mortality of surgically treated trauma patients with an ankylosing spinal disorder was high compared to previously healthy individuals with traumatic spine fractures. A total of 17.7% from the cohort of patients with AS and 20.0% from the patients with DISH deceased within three months after injury whereas the previously reported mortality in individuals treated surgically for traumatic spinal fractures was only 0.4%.[228] The mortality in the follow up phase was higher in DISH patients than in AS patients, regardless of type of treatment received. Several authors have stated that advancing age, obesity and

diabetes mellitus are associated with higher mortality rates in trauma patients.[27;85;94;100;135;144;154] In addition, some authors have reported the treatment with a halo frame or other immobilization device in elderly patients with cervical fractures to be associated with higher morbidity and mortality rates.[86;134;214] Finally, it is also known from the literature that surgery in elderly people is associated with higher rates of morbidity and mortality probably due to preexisting medical conditions.[74;87;174] Since DISH has been associated with obesity, type 2 diabetes and advancing age, this could explain the higher mortality.[41;108]
The prevalence of AS is stable and is estimated to be 0.05 – 1.4%.[21] Studies investigating DISH have found a prevalence ranging from 2.9% to 25% in selected populations.[106;234] Acknowledging the association of DISH with typical traits of modern affluent societies (obesity and diabetes for example) its prevalence and degree of expression can be expected to increase during the coming decades, therefore clinicians should be prepared to admit more trauma patients with DISH.[41;108;202;240] Recognizing the limitations of the current study, we suggest the following conclusions can be drawn (Level of Evidence 4; Grade of Recommendation C):[161]

- Patients with an ankylosed spine have an increased fracture risk even after minor trauma
- Delayed diagnosis of fractures in patients with ankylosing spinal disorders often occur, due to both doctor and patient related factors
- Fractures of the ankylosed spine tend to be unstable, because ossified ligaments and surrounding tissue also fracture
- An intrinsic unstable fracture configuration may lead to primary and secondary neurological deficit
- The clinical outcome of patients fracturing their ankylosed spine is worse compared to the general spine trauma population
- Surgical treatment may be favorable for patients with an ankylosed spine and spinal fracture, as this treatment option may be associated with lower complication and mortality rates and may lead to neurological improvement more frequently
- The presence of ankylosed spine segments should alert the treating physician for unstable spine fractures in every trauma patient
- In trauma registries ankylotic conditions of the spine should be registered separately, in order to acquire more knowledge on the patterns and prognosis of these injuries
- As DISH may be a rapidly increasing condition in affluent societies, awareness of this condition should be raised among physicians assessing trauma patients and treating spinal injuries

CHAPTER 3

The prevalence of diffuse idiopathic skeletal hyperostosis in an outpatient population in the Netherlands

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J Rheumatol 2008;35(8):1635 – 8

Abstract

Background

In diffuse idiopathic skeletal hyperostosis (DISH) spinal ankylosis may occur due to ossification of spinal longitudinal ligaments. DISH can lead to back pain, impaired mobility and unstable spinal fractures after minor trauma. Its etiology is unknown but is associated with obesity and type 2 diabetes mellitus. This study was conducted to provide information on the present-day prevalence of DISH in an outpatient population in the Netherlands.

Methods

The chest radiographs of 501 patients (> 50 years of age), referred by general practitioners to our institution for a first consultation for non-spine-related conditions, were reviewed. DISH was established according to the criteria of Resnick and Niwayama; three level involvement was defined as pre-stage DISH and regarded as the precursor of full blown DISH. Logistic regression analysis was performed to investigate the influence of age and gender on the prevalence of DISH.

Results

The overall prevalence of DISH was 17.0% (95% CI 13.7 - 20.3). A significant increase with age was observed; the odds ratio of age was 1.03 (95% CI 1.01 - 1.05; $p = 0.006$). The odds ratio of male gender was 1.85 (95% CI 1.20 - 2.86; $p = 0.006$). The individual predicted probability of developing DISH was 32.1% in 80-year-old males and 16.9% in females of the same age. Pre-stage DISH was found in 4.6% of the individuals and was more frequent in females.

Conclusions

The overall prevalence of DISH in this outpatient cohort was 17.0%, which is high compared to recent literature. Logistic regression analysis demonstrated age and gender to be significantly related to the presence of DISH; suggesting that males and older individuals have a higher probability of developing DISH. Since DISH is associated with metabolic abnormalities such as obesity and type 2 diabetes mellitus, that seem to become endemic in modern-day societies, DISH may become a more prevalent and therefore more important condition in the future.

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a common musculoskeletal disorder in which ligaments and entheses slowly become ossified, eventually leading to decreased mobility of the affected region.[179] DISH is observed mostly in the elderly and demonstrates a male predominance.[14] Its etiology is unknown, but is associated with obesity and type 2 diabetes mellitus.[41;108] DISH has received little attention in clinical literature compared to other ankylosing disorders such as ankylosing spondylitis (AS), probably since its symptoms are usually mild, consisting of minor back pain and/or a slight loss of function.[138;177] More serious complications of DISH, however, have also been described such as myelopathy and spinal canal stenosis.[168;205] Similar to patients with AS, patients with DISH may experience complete spinal ankylosis. Fusion of multiple spinal segments subsequently leads to stiff and long lever arms on which forces can act, potentially leading to displaced and unstable fractures, even after minimal trauma.[25;40;164] Since patients with DISH may display a history of back pain and interpretation of their radiographs can be difficult due to pathological osseous changes, they have an increased risk of delayed fracture diagnosis.[80]

Prevalences of DISH range from 2.9% in a Korean population to 25% in Caucasian men in the USA.[106;234] Since the articles of Julkunen *et al.* in 1975 and 1981, the most recent Western European data have been published by Pappone *et al.*; reporting a prevalence of 15.1% in a cohort of Italian women.[96;98;167] Acknowledging that DISH may be associated with type 2 diabetes, obesity and advanced age, all typical traits of modern affluent societies, its prevalence can be expected to increase during the coming decades.[202;240] We assessed the current prevalence of DISH in an outpatient population of individuals over 50 years of age in the Netherlands and calculated the individual predicted probability of developing DISH.

Methods

The radiographs of all patients over 50 years of age visiting the outpatient clinic of the Department of Internal Medicine for a first consultultation from October 2004 until October 2006 were selected from the radiological database of our institution by means of a coding system. All patients were referred to the outpatient clinic by general practitioners for various medical conditions. From this group consisting of 1065 patients, the posteroanterior (PA) and lateral chest radiographs of the first 501 consecutive patients (in alphabetical order) were reviewed by two authors (LAW and HMEQvU). In case consensus on the diagnosis could not be reached, a third investigator (JJV) was consulted. The original radiological reports were retrieved for formal assessment of thoracic pathology.

All chest radiographs were acquired with computed radiography equipment (Optimus ZP33; Philips Medical Systems, Eindhoven, the Netherlands), using a standardized technique (125 kV with 2 lateral fields; 200-cm film-focus distance). The images were examined with a Picture Archiving and Communication System (PACS) viewer (Philips

Table 1
Prevalence of DISH stratified in 10-year age groups: number of patients (percentage; 95% confidence interval).

	Age group			
Status	**50 – 59**	**60 – 69**	**70 – 79**	**80+**
No DISH	139 (84.8; 79.3-90.3)	97 (77.0; 69.6-84.3)	108 (74.5; 67.4-81.6)	49 (74.2; 63.7-84.8)
Pre-stage DISH	7 (4.3; 1.2-7.4)	8 (6.3; 2.1-10.6)	3 (2.1; -0.25-4.4)	5 (7.6; 1.2-14.0)
DISH	18 (11.0; 6.2-15.8)	21 (16.7; 10.2-23.2)	34 (23.4; 16.6-30.4)	12 (18.2; 8.9-27.5)
Total	**164 (100.0)**	**126 (100.0)**	**145 (100.0)**	**66 (100.0)**

Medical Systems, Eindhoven, the Netherlands) with a 1536x2048-pixel monitor able to display 256 shades of grey (3MP2FH; Barco, Kortrijk, Belgium). Tools regularly used in PACS were threshold, zoom and invert.
DISH was established when the radiological criteria of Resnick and Niwayama were fulfilled on the PA or lateral view or both.[178] Ossification of the anterior longitudinal ligament over three contiguous vertebral bodies (*i.e.* two discs bridged) was considered to be the likely precursor of full blown DISH and defined as 'pre-stage DISH'; this was recorded separately to provide insight in the natural course and progression of DISH. Individuals with inconclusive radiographs were, regardless of cause, scored as non-DISH subjects. SPSS (version 12.0.2) was used for statistical evaluations. Logistic regression analysis was performed to investigate the influence of age and gender on the prevalence of DISH. To differentiate correctly in this analysis, individuals diagnosed with pre-stage DISH were regarded as non-DISH subjects. Finally, the individual predicted probability of developing DISH was calculated. In this statistical analysis which was directly retrieved from the logistic regression model, the individual predicted lifetime risk of developing DISH, according to age and gender, was calculated.

Results

The mean age of all study subjects was 66.6 ± 10.7 years; 45.7% of the study subjects was male. The mean age of individuals with defined DISH was 69.6 ± 10.0 years, vs. 66.0 ± 10.8 years for subjects not displaying DISH. The overall prevalence of DISH in this cohort was 17.0% (95% CI 13.7 - 20.3). Prevalence increased with advancing age to 23.4% (95% CI 16.6 - 30.4) in patients 70 - 79 years of age (table 1). DISH was established in 22.7% (95% CI 17.3 - 28.1) of the males and in 12.1% (95% CI 8.3 - 16.0) of the females of the entire group (table 2). Pre-stage DISH was found in 4.6% (95% CI 2.8 - 6.4) of subjects and was more frequent in females. The male/female ratio of DISH was 1.6:1, in pre-stage DISH it was 0.6:1. The overall male/female ratio in this cohort was 0.8:1. Logistic regression analysis showed that both male gender and age were significantly related to the presence of DISH. The odds ratio for gender was 1.85 (95% CI 1.20 - 2.86; p = 0.006). For increasing age the odds ratio was 1.03 (95% CI 1.01 - 1.05; p = 0.006), demonstrating males and older individuals to have a higher probability of developing DISH. The relationship between

Table 2
Prevalence of DISH according to gender: number of patients (percentage; 95% confidence interval).

Status	Female	Male	Total
No DISH	225 (82.7; 78.2-87.2)	168 (73.4; 67.6-79.1)	393 (78.4; 74.8-82.0)
Pre-stage DISH	14 (5.2; 2.5-7.8)	9 (3.9; 1.4-6.5)	23 (4.6; 2.8-6.4)
DISH	33 (12.1; 8.3-16.0)	52 (22.7; 17.3-28.1)	85 (17.0; 13.7-20.3)
Total	**272 (100.0)**	**229 (100.0)**	**501 (100.0)**

age, gender and the probability of developing DISH is depicted in figure 1. Males 60 years of age, for instance, have an individual predicted probability of developing DISH of 18.8%; by the age of 80 this risk is increased to 32.1%. Females have 9.1% chance of having DISH when they are 60 years old; by the age of 80 years this risk has almost doubled, to 16.9%.

The diagnosis DISH was not described in any of the radiological reports. In 97.6% of the affected subjects the diagnosis DISH could be established on the PA radiograph, vs. 40.0% on the lateral view. In two cases DISH was detectable on the lateral view only. In 36 patients (7.2%) radiological assessment of DISH was inconclusive because of superimposition of intrathoracic structures and/or poor radiographic quality.

Discussion

In this study of 501 subjects over 50 years of age visiting the outpatient clinic of internal medicine of our institution for various unrelated conditions, we found the overall prevalence of DISH to be 17.0%, which is high compared to the available literature. The most recent data concerning the prevalence of DISH in a Western European society are from Pappone *et al.*, who reported a prevalence of DISH of 15.1% in a cohort consisting of 93 Italian females over 40 years of age.[167] Their results are comparable to the findings for our cohort of females.

Julkunen *et al.* performed a large population based study in the early 1980's, in a cohort of 9000 individuals over 40 years of age, which was representative for the general population of Finland.[96;98] They found hyperostosis in 3.8% of males and 2.6% of females. Unfortunately, they did not use the formal Resnick criteria in their survey and the methodology of their study differs considerably from ours, making the results less comparable and difficult to interpret. Kiss *et al.* reported a high prevalence in their epidemiological survey in Budapest, Hungary, in 2002.[107] Using the modified Resnick 2 criterion (two level bridging over three adjacent vertebral bodies) they found DISH to be present in 27.3% of males and 12.8% of females.[96] In our study two level bridging was defined as pre-stage DISH, because it was considered to be the precursor of actual DISH; this was present in 4.6% of our subjects. Three level bridging over four contiguous vertebrae, meaning DISH as originally stated by Resnick and Niwayama, was present in

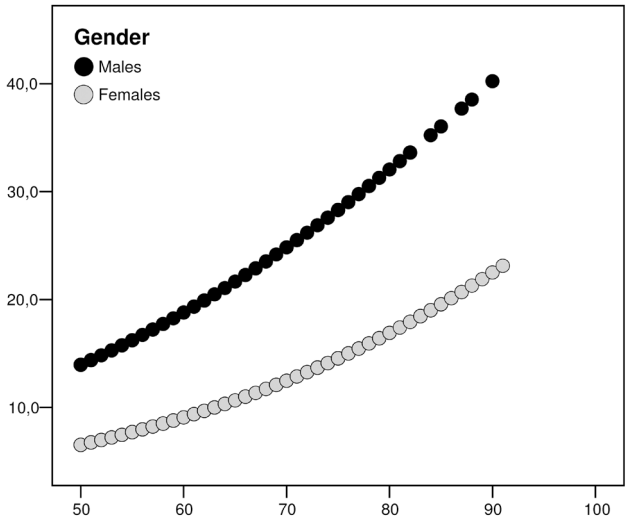

Figure 1
Individual predicted probability of developing DISH, according to age and gender.

6.1% of males and in 1.2% of females in the cohort described by Kiss and coworkers. The difference in prevalence of DISH between their report and our study could result from the fact that their oldest patient group was 70 - 79 years, while we included patients over 80 years as well. Furthermore, modern lifestyle related diseases such as obesity and type 2 diabetes mellitus, both associated with the development of DISH, have appeared in Western European countries like the Netherlands decades earlier than most Eastern European countries arguably explaining another important factor for this difference in prevalence.[240]

Weinfeld *et al*. studied more than 2300 hospitalized and outpatient individuals from two different hospitals in Minneapolis, USA, in 1997, using the formal Resnick criteria and found a prevalence of 25% in males and 15% in females.[234] The prevalence results from our outpatient population are comparable to theirs, suggesting exposure to similar risk factors for developing DISH in North America and Western Europe. Interestingly, we found a higher prevalence of pre-stage DISH in females than in males (male/female ratio of 0.6:1). Although there were no women with pre-stage DISH in the group 70 - 79 years, the trend indicates that the prevalence of pre-stage DISH also increases with age. It seems likely that in males, DISH develops at a younger age, demonstrates a higher prevalence at any given age compared to females and progresses faster than in females as well. In women, ligament ossification probably starts later in life and does not always progress into fully developed DISH.

A posteroanterior (PA) chest radiograph may be a reliable screening tool to diagnose DISH. In our study DISH could be established on the PA chest radiograph in 97.6% of subjects. DISH was detectable on the lateral view in 40.0%. Thus, we suggest that a standard PA chest view is an easily obtainable screening tool to diagnose DISH in a clinical setting.

Acquiring both PA and lateral views, however, could further increase the sensitivity of this instrument.[139] In cases where radiographic interpretation is difficult due to projection of thoracic structures or poor quality of the radiograph, a lateral thoracic radiograph could add extra diagnostic information.

The focus on specific cardiac/pulmonary/abdominal pathology in this series of chest radiographs could explain the absence of the diagnosis of DISH in the original radiological reports. It is likely that the attention of the examining radiologist was on the intrathoracic structures, rather than on skeletal pathologies, when pursuing the clinical questions. However, low level of awareness for DISH cannot be ruled out.

The etiology of DISH remains unknown, but associations with metabolic disorders such as type 2 diabetes mellitus and obesity have been suggested.[41;108] Since these conditions seem to have become endemic in Western societies due to lifestyle, DISH could become a more frequent and therefore more important disease in the coming decades.[202;240]

CHAPTER 4

Quantitative analysis of the anterolateral ossification mass in diffuse idiopathic skeletal hyperostosis of the thoracic spine

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Eur Spine J 2011;20(9):1474 – 9

Abstract

Background

Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic condition leading to ossification of spinal ligaments and may behave similarly to ankylosing spondylitis (AS), often leading to unstable hyperextension fractures. There are no quantitative data available on the spatial characteristics of the ossifications, to clarify the propensity in DISH to fracture through the vertebral body instead of through the IVD as seen in AS; or to explain the typical 'flowing wax' morphology observed in DISH.

Methods

Quantitative analysis of the bridging anterolateral ossification mass (ALOM) area and centroid angle at the mid-vertebral body level; IVD level and in between levels was performed on computed tomography (CT) data from ten human cadaveric specimens with DISH. Additionally, the localization of the vertebral segmental arteries (VSAs) and the relation between their localization and the ossifications was verified using computed tomography angiography (CTA) data from ten patients with DISH and ten controls.

Results

The ALOM area at the mid-vertebral body level averaged 57.9 ± 50.0 mm^2; at the level of the IVD it averaged 246.4 ± 95.9 mm^2. The mean ALOM area at the adjacent level caudal to the mid-vertebral body level was 169.6 ± 81.3 mm^2; at the cranial level it was 161.7 ± 78.2 mm^2. There was a significant difference between mean ALOM area at the mid-vertebral body level and other three levels ($p < 0.0001$). At CTA the VSAs were localized at the mid-vertebral body level in nearly all images, irrespective of the presence of DISH.

Discussion

The ossification was maximal at the level of the IVD and smallest at the mid-vertebral body level. The VSAs could be located at the mid-vertebral body level in nearly all patients of both DISH cases and controls. The results from the present study possibly explain the tendency for fractures through the vertebral body in DISH and a role for the arterial system in the inhibition of soft tissue ossification.

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic condition leading to ossification of ligaments and entheses.[127;178] A hallmark of DISH is the flowing ossification (often compared to flowing candle wax) of anterolateral soft tissue over at least four contiguous vertebral bodies, most frequently found in the thoracic spine.[178] Clinical symptoms resulting from DISH are mainly due to altered biomechanics and may lead to a decreased range of motion and painful stiffness of the structures affected.[129;179] Direct compression of surrounding tissues by the progressively growing bony mass in the cervical spine has led to several cases of dysphagia, airway obstruction and radicular complaints.[159] Furthermore, advanced forms of spinal DISH have shown to behave similarly to ankylosing spondylitis (AS), increasing the chance for unstable spine fractures four- to eightfold compared to a general population, even after low energy trauma.[40;164] In a recent systematic review of the literature on the clinical outcome of patients with fractures of the ankylosed spine, an unusually high percentage of hyperextension type fractures (74.4% of all fractures in AS and 51.2% of all fractures in DISH) was found, sharply contrasting the percentage of 0.2% hyperextension fractures (type B3, according to the AO classification) found by Magerl *et al.*, in their pivotal study of 1445 spine fractures.[133;236] Remarkably, the planes of the fractures sustained by patients with DISH were more frequently located through the vertebral body than through the disc (figure 1). As the predilection place for fractures in AS seems to be the opposite, the two ankylosing disorders may constitute different biomechanical configurations with distinct modes of failure.[25]

Figure 1
Sagittal reconstruction of a CT scan of a 68-year old female pedestrian who was hit from behind by a motor vehicle, demonstrating DISH at the levels T5 – T10 and a T10 hyperextension fracture through the vertebral body.

Currently, no quantitative data are available on the spatial relationship between the bridging anterolateral bony mass and the vertebral body/intervertebral disc in DISH to explain the different fracture pattern compared to AS. Additionally, no reasonable explanation beyond speculation has been published for the development of the typical, right-sided 'flowing candle wax' morphology, as observed in DISH. The hypotheses of the present study were therefore twofold:

1. The spatial characteristics of newly formed osseous structures in DISH may be responsible for the higher incidence of fractures through the vertebral body rather than through the disc space.
2. The presence of the arterial vascular system may provide a natural barrier for new bone formation in DISH.

To answer the first hypothesis, the extent and localization of DISH were investigated by quantifying the transverse area and centroid (geometric center) of the anterolateral ossified mass on computed tomography (CT) data obtained from ten human cadaveric thoracic spines with DISH. To test the second hypothesis, the results obtained from the first experiment were verified by localizing the vertebral segmental arteries (VSA) on computed tomography angiography (CTA) data of ten patients with DISH and subsequently compared to ten controls.

Methods

Investigating the extent and localization of DISH

A total of 89 embalmed human cadaveric thoracic spines, stripped from their surrounding soft tissues, were obtained from the Dept. of Anatomy of our institution and screened for DISH, by two independent observers, by macroscopical inspection and fluoroscopy (Omnidiagnost Eleva; Philips Medical Systems, Best, the Netherlands) using the criteria of Resnick and Niwayama.[178] The absence of sacroiliac erosion was not considered an absolute requirement for this part of the study since these joints were not available for screening in the specimens obtained. A total of ten specimens (five male / five female donors, on average 80.4 years old, ranging from 66 to 91 years) met the criteria and underwent CT scanning to:

1. Establish a definite diagnosis of DISH (excluding AS and other osseous abnormalities).
2. Perform quantitative analysis of the anterolateral ossifications.

Scanning was performed in supine position with a 64-slice scanner (Philips Brilliance; Philips Medical Systems, Best, the Netherlands), using 0.625 cm axial helical scans with high resolution (120 kV, 200 mAs, slice thickness 0.9 mm). On sagittal and coronal reconstructions, the level of interest was determined by identifying and recording the

first four contiguous spinal levels connected by an anterolateral ossification mass (ALOM), counting from the twelfth thoracic vertebra and moving cranially. From all four-segment specimens thus identified, the mid-vertebral body level, intervertebral disc space level and in-between levels were visualized. See also figure 2 for a detailed illustration of the location of the levels under study. A total of 130 CT images (ten specimens x 13 transverse planes) were captured in .bmp format (768 x 765 pixels) and subsequently imported to, and analyzed by, 2D/3D modeling software (Rhinoceros® version 3.0, Seattle, USA). First, the anteroposterior (AP) axis was defined by the line drawn from the most ventral to the most dorsal part of the vertebral body/disc.

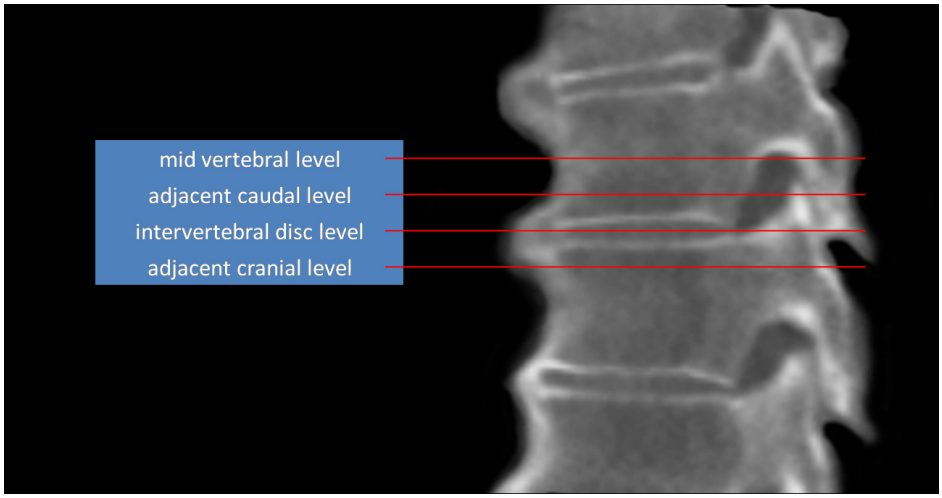

Figure 2
Sagittal reconstruction of a CT scan of a human cadaveric spine with DISH demonstrating the transverse levels used for quantitative measurements (the description cranial or caudal is relative to the closest mid-vertebral level).

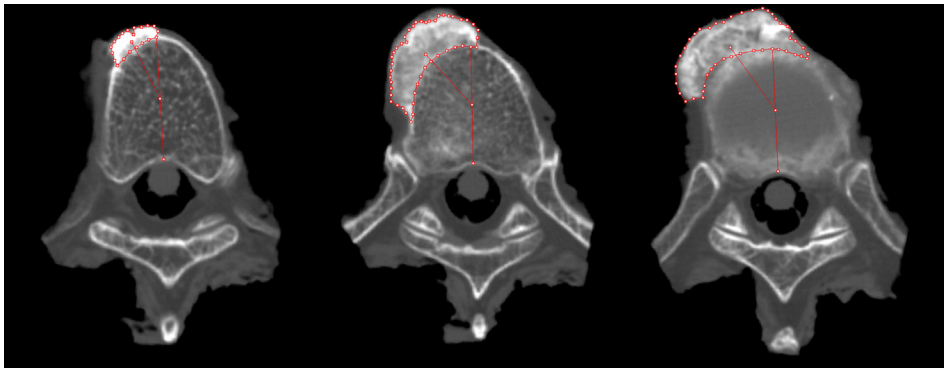

Figure 3
Transverse CT images from one specimen showing the graphical method used to define the ALOM and angle between the centroid and anteroposterior axis (left at mid-vertebral level; middle at adjacent cranial level; right at IVD space level).

This AP line was bisected to create a vertebral body center node (VBC). Multiple nodes (up to 50) were subsequently drawn manually to outline the ALOM and a connecting line was drawn through these nodes (see figure 3). The centroid node (geometrical center; CN) of the ALOM was calculated and automatically drawn by the software and a line was drawn from the CN to VBC in order to measure the angle of this line relative to the AP axis, called the anteroposterior-centroid node angle (AP-CN angle). Finally, a line was drawn over the CT-generated ruler to convert to a real-world dimension (mm). Total ALOM area was calculated by the software (in mm^2) as was the AP-CN angle (in °, where a positive value was assigned to all orientations pointing to the right side of the body, *i.e.* counter-clockwise from the AP axis, and a negative value assigned to orientations pointing to the left side of the body, *i.e.* clockwise from the AP axis).

Localization of vertebral segmental arteries in DISH and controls

The results from the first experiment were verified using CTA data (using the same scanner and scanning protocol described above) obtained from 20 patients examined previously for aneurysms of the abdominal aorta, ten of whom also had DISH according to the full set of Resnick criteria (all male, age on average 71.4 years, ranging from 57 to 85 years) while the diagnosis DISH was definitely ruled out for the other ten patients (all male, age on average 68.9 years, ranging from 58 to 80 years) again by two independent observers.

The tenth thoracic vertebra, a level frequently involved in DISH and present in the majority of the cadaveric specimens used, was identified on the CTA scans and coronal images were obtained from the following three locations: the anterior vertebral body wall; the center of the vertebral body and the plane in-between (see figure 4). On these images the right-sided VSA was identified and its cranial-caudal location was recorded using the same levels as for the cadaveric experiment: at the mid-vertebral body level, intervertebral disc space level and in-between adjacent levels.

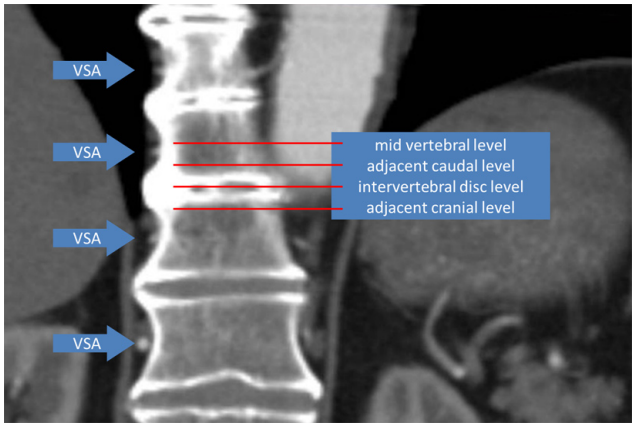

Figure 4
Coronal reconstruction of a CTA scan of a patient with DISH demonstrating the method of locating the vertebral segmental artery (VSA).

Statistics

A repeated measures analysis with two within factors (affected vertebral level (T_n) and measurement localization) was used to examine the main effects of these two factors but also to assess whether these effects depend on each other (interaction between vertebral level and measurement localization). If there was a significant main effect, a post hoc analysis with *Bonferroni* adjustment was performed. For the measurement localization as well as for the vertebral levels, the most cranial location/level respectively, was compared with all others. Statistical significance was set at $p < 0.05$.

Results

Investigating the extent and localization of DISH

ALOM, bridging (at least) four levels, was found at T6 – T9 (in three specimens); T7 – T10 (four specimens) and T8 – T11 (three specimens). The ALOM area at the mid-vertebral body level from T6,T7,T8,T9,T10 and T11 averaged 57.9 ± 50.0 mm^2; at the mid intervertebral disc space level from T6 – T7, T7 – T8, T8 – T9, T9 – T10 and T10 – T11 it averaged 246.4 ± 95.9 mm^2. The mean ALOM area at the adjacent level caudal to the mid-vertebral body level was 169.6 ± 81.3 mm^2; the mean ALOM area at the adjacent cranial level was 161.7 ± 78.2 mm^2. No interaction was found between vertebral level and measurements ($p = 0.19$) and no main effect was found for vertebral level ($p = 0.63$). However, there was a significant main effect of measurement localization ($p < 0.001$). The results of the several levels were statistically indifferent from each other ($p > 0.6$) but the measurements within these levels were statistically different ($P < 0.001$). The main finding was the significant difference between mean ALOM area at the mid-vertebral body level and the other three levels ($p < 0.0001$). See also figure 5 for a graphical representation of the results. The mean AP-CN angle at the mid-vertebral body level was 32.5° ± 25.4°; at the mid intervertebral disc space level it was 43.7° ± 18.1°. The mean AP-CN angle at the adjacent level caudal to the mid-vertebral body level was 41.3° ± 23.3°; at the adjacent level cranial to the mid-vertebral body level it was 46.8° ± 22.9°. There was no interaction between level and measurements ($p = 0.33$) and also no main effect of vertebral level ($p = 0.10$). A trend was found towards a main effect of the measurement localization, but it was not statistically significant ($p = 0.06$). The results of the several levels were statistically indifferent from each other ($p > 0.1$). The several measurements within these levels were statistically indifferent from each other ($p > 0.1$).

Localization of vertebral segmental arteries in DISH and controls

The VSA could be identified on all 30 images in the DISH group (n = 10 cases with three images each) and also on the 30 images in the control group. In all DISH cases the VSA was located at the mid-vertebral body level or between the mid-vertebral body level and adjacent caudal level. In the control group the VSA was located at the mid-vertebral body level or between the mid-vertebral body level and adjacent caudal level in 29 images; in one image (located on the anterior vertebral wall) it was at the adjacent caudal level.

No significant differences were found between the DISH group and controls regarding the location of the VSA.
In summary, the mean area of ALOM was the largest at the disc space level and smallest at the mid-vertebral body level. The vertebral segmental artery could be located in the coronal plane at, or approximately at, the mid-vertebral body level in nearly all images (59 out of 60) of both DISH cases and controls. A larger area of ALOM was associated with a trend toward increased counter-clockwise rotation of the centroid of this mass relative to the AP axis.

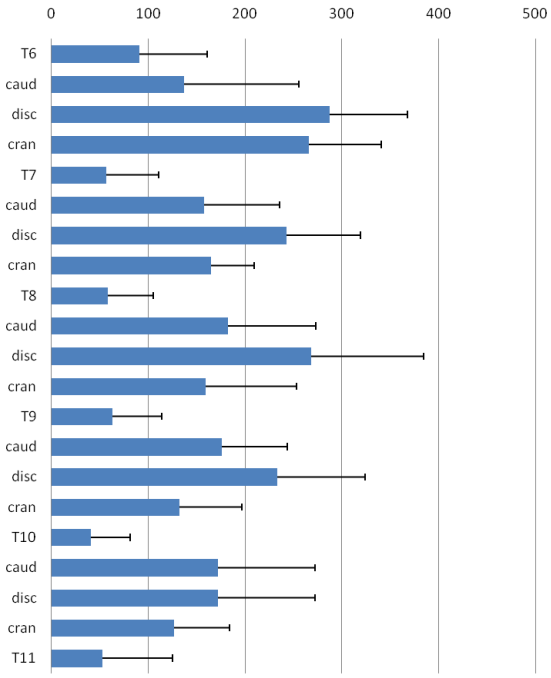

Figure 5
Graph demonstrating mean area of ALOM values and standard deviations (in mm^2) for the individual levels.

Discussion

In the first part of this study, the mean area of the ALOM and its centroid-to-AP axis angle was quantified at the mid-vertebral body level; mid intervertebral disc level and in-between adjacent caudal/cranial levels. It was demonstrated that a significant difference in mean ALOM area exists between these levels, displaying the largest ALOM area at the intervertebral disc level and smallest ALOM area at the mid-vertebral body level. This finding could help explain the previously published high prevalence of (hyperextension-) fractures *through the vertebral body* in DISH compared to the *through-disc* fracture pattern more frequently seen in AS.[236] Although little is known about the histology, ultrastructure

or yield strength of the ossified soft tissue mass in DISH, it seems plausible that the significantly larger area of ALOM at the intervertebral disc space level and caudal/cranial adjacent levels compared to the mid-vertebral body level could account for the solid bridge between two adjacent endplates leaving the mid-vertebral level the weakest link. Moreover, a series of anteriorly connected (*i.e.* ankylosed) vertebral segments could lead to long lever arms on which relatively minor traumatic forces could act to result in hyperextension type fractures (figure 1).[80] The disproportionally large number of hyperextension fractures in DISH relative to compression or flexion fractures (comprising the majority of spinal fractures) is not readily explained by this hypothesis, however.

The counter-clockwise position of the ALOM centroid relative to the AP axis was found to be positively associated with the extent of ALOM area, although this finding did not reach statistical significance. This finding corroborates previously postulated suggestions that the presence of the pulsating aorta prevents DISH from forming.[175] The right-sided localization of the ALOM is highly suggestive for an aortic natural barrier, as is the fact that ALOM 'growth' can, apparently, only take place more distant (*i.e.* counter-clockwise) from this vascular structure. Indeed, previous studies in individuals with *situs viscerum inversus* and DISH, found ALOM formation at the left-side (clockwise) position of the vertebral body.[35] Building further on the hypothesis that only limited amounts of new bone form in the vicinity of a pulsating vascular structure, the results from the cadaveric experiment, showing significantly less new bone formation at the mid-vertebral body level, needed verification by identifying such a structure at that location. The clinical CTA study showed the location of the VSA, indeed, to be situated at (or approximately at) the level of the mid-vertebral body in both DISH cases and controls.[200] This finding strongly suggest the VSA to be a fixed natural barrier for the expansive ossification process possibly dictating the typical 'flowing candle wax' appearance of DISH. It can be argued that CTA data from patients under monitoring for aneurysms of the abdominal aorta might not represent the ideal substance for this study since a preexistent vascular disease could have direct altering effects on the location, orientation and diameter of branching vertebral segmental arteries. However, to our knowledge, no association between abdominal aneurysms and aberrant vertebral segmental arteries has yet been reported and this potential study limitation has, therefore, not been judged overtly relevant.

Concluding, in DISH, the mean ALOM and centroid angle of the ALOM vary considerably at the mid-vertebral, IVD and in-between adjacent levels. The results from the present study suggest a predisposition for fractures through the vertebral body and a role for the arterial system in the inhibition of soft tissue ossification in DISH.

CHAPTER 5

The influence of diffuse idiopathic skeletal hyperostosis on bone mineral density measurements of the spine

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Rheumatology (Oxford) 2009;48(9):1133 – 6

Abstract

Background

Bone mineral density (BMD) has been described to be increased in patients with diffuse idiopathic skeletal hyperostosis (DISH). The exact contribution of the ossified anterior longitudinal ligament (ALL) on vertebral body BMD is currently unknown. We quantitatively investigated the influence of DISH on BMD measurements using an experimental dual energy X-ray absorptiometry (DXA) scanning protocol.

Methods

Ten human cadaveric spines showing distinctive features of DISH according to the Resnick criteria and ten matched control specimens were used. After assessment of the localization and orientation of the ossified ALL with computed tomography, BMD was measured using an experimental DXA protocol, either including or excluding the ossifications from the scanningfield. For controls, identical orientations were used and both groups were compared for differences in BMD.

Results

The mean age at death of the DISH specimens was 80.4 ± 8.2 years and 81.0 ± 6.9 years in controls ($p = 0.382$). Specimens with DISH displayed a significantly higher BMD than their matched controls whenever the ossified ALL was present in the scanning field. The contribution of the ossification ranged from 23.6% to 30% in various scanning orientations. Measurements of the left half of the spine, where most of the ossified ligament was outside the scanning field, did not statistically differ in DISH specimens and controls ($p = 0.446$). The right-left difference in anteroposterior view was statistically significant within DISH specimens ($p = 0.001$), but not in controls ($p = 0.825$).

Conclusions

The variability in measurements in different scanning orientations suggests a substantial contribution of the ossified ALL to the total BMD in DISH specimens, ranging from 23.6% to 39.0%. Vertebral body BMD does not seem to be increased, as demonstrated by comparable BMDs in the unaffected left half of the spine. It is suggested that routine anteroposterior DXA scanning may overestimate the true *vertebral* body BMD in DISH patients.

Introduction

In diffuse idiopathic skeletal hyperostosis (DISH), spinal and peripheral ligaments and entheses become ossified.[179] Most clinical symptoms of DISH are mild, although serious complications are being reported with increasing frequency including myelopathy, unstable thoracolumbar fractures after minor trauma and complaints such as dysphagia and dyspnoea due to bony protrusions of the cervical spine.[46;80;140;205;236] Extraspinal manifestations consist of tendonitis and painful enthesophytes, which are often bilateral and symmetrical.[14] The etiology of DISH is not known although several authors have proposed an association with increasing age, obesity and type 2 diabetes mellitus.[41;108] Reported prevalences range from 2.9% in Korea to 25% in Caucasian men in the USA and may well increase the coming decades because of the relation between DISH and modern lifestyle related diseases like obesity and diabetes.[106;234] Since DISH particularly affects the right side of the anterior longitudinal ligament (ALL), it has been hypothesized that pulsations of the aorta may prevent ossification on the left side.[64] This hypothesis is supported by the few cases of individuals with situs viscerum inversus and DISH, where ossifications of the ALL were found on the left side of the spine.[31;35]

The definition of DISH suggests a generalized state of hyperostosis and the exuberant ossifications of the thoracic spine displayed on chest radiographs could lead to an impression of skeletal robustness.[186] In accordance with this impression, bone mineral density (BMD) of patients with DISH has been described to be increased compared to unaffected individuals.[43;76;186] In these studies, BMD was established with the metacarpal index (MCI) on conventional radiographs of the hand; dual energy X-ray absorptiometry (DXA) of the distal radius and DXA of the lumbar spine. An anteroposterior DXA scan of the lumbar spine may, however, not be a reliable method to establish BMD of vertebral bodies in DISH patients as the ossified ALL may well project in the field of view during DXA scanning, thereby possibly leading to an overestimation of BMD. This may lead to adverse clinical strategies, for instance, when osteoporosis goes undetected due to overestimation of the true vertebral BMD.

To the author's best knowledge, no studies have been published investigating the influence of DISH on BMD measurements of the spine. In the current study, we quantitatively investigated the contribution of the ossified anterior longitudinal ligament on calculated vertebral body BMD in ten human cadaveric spines with DISH and ten control specimens without DISH and subsequently estimated the real vertebral BMD of spines affected by DISH.

Methods

Identification and preparation of specimens

From the Department of Anatomy, 20 formaldehyde fixed (4%) human thoracolumbar spines were obtained. The spines were obtained from individuals who donated their body for the benefit of science. We selected ten specimens that showed definite features of

DISH, according to criteria defined by Resnick and Niwayama at fluoroscopical examination (Omnidiagnost Eleva; Philips Medical Systems, Best, the Netherlands) and comprising of flowing ligamentous ossification along the anterolateral aspect of at least four contiguous vertebral bodies with preservation of intervertebral disk height at the involved segment and absence of extensive degenerative changes.[178] Another ten age- and gender matched specimens without signs of DISH were selected as controls. The spines were stripped from all soft tissues, except for the ligaments and intervertebral disks and the ribs were subsequently removed. A regular off-the-shelf chipboard screw (6.0 x 120 mm) was drilled in each 12th thoracic vertebra to serve as reference during computed tomography (CT) and DXA scanning. See figure 1 for a schematic representation of the workflow of the study.

CT scanning

CT scanning with sagittal/coronal multi-planar reformatting was performed on a 64-slice scanner (Philips Brilliance; Philips Medical Systems, Best, the Netherlands), using 0.625 cm axial helical scans with high resolution (120 kV, 200 mAs, slice thickness 0.9 mm). The three most central and prominent bony bridges, spanning four vertebral bodies, were marked as region of interest (ROI). For the control samples, ROIs identical to the DISH specimens were recorded. Controls with moderate osteophytes present at the ROI were not excluded, since the Resnick criteria also allow for the diagnosis DISH in the presence of 'localized pointed excrescences'.[178] The following parameters were assessed on transverse CT images for the two most central vertebral bodies of the ROI in the DISH specimens:

1. Anteroposterior (AP) axis, defined as the line through the middle of the anterior cortex of the vertebral body and the centre of the vertebral body (figure 2A; vertical yellow line).
2. Line from the outer left, to the outer right border of the ossified ALL (figure 2A; red line).
3. Angulation of the line through the midportion of the ossified ALL relative to the AP axis (clockwise or counterclockwise), measured in degrees (figure 2A; yellow/green shaded triangle).
4. Transverse orientation of the previously inserted screw in the 12th thoracic vertebra relative to the AP axis, measured in degrees.

DXA scanning

From the above data the experimental DXA scanning orientations were calculated for all DISH specimens individually and identical scanning orientations were used for the matched controls. A frame was designed to hold the specimen in the desired orientation while avoiding obstruction of the scanning field (figure 3). A 'routine' BMD was first established by AP DXA scanning to provide reference values for the four vertebral bodies in each ROI (Hologic QDR-4500 Discovery A, software version 12.3; Hologic Inc., Bedford, MA, USA).

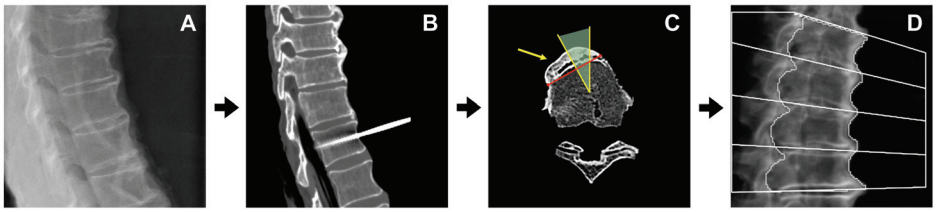

Figure 1
Schematic representation of the workflow of the present study.
A Fluoroscopy: diagnosis of DISH according to Resnick criteria. **B** CT scanning: identification of ROIs (the three most central and prominent bony bridges spanning four vertebrae) in sagittal plane; for controls identical ROIs were used. **C** Planning of DXA scans: calculation of different experimental DXA scanning orientations in DISH specimens on transverse CT images. **D** DXA scanning: BMD measurements in different experimental orientations; identical for DISH and controls.

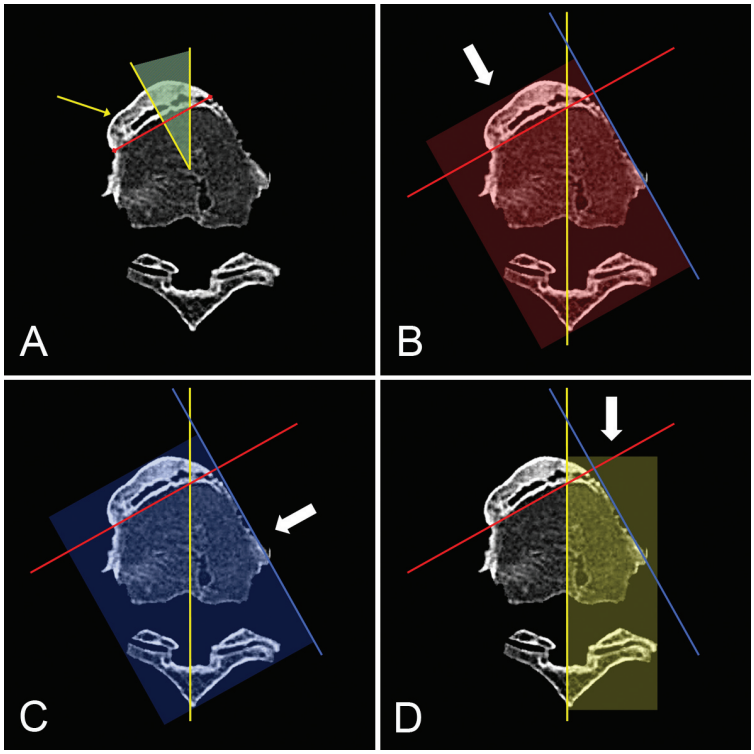

Figure 2
Landmarks on transverse CT image of DISH specimen.
A yellow arrow ossification of the ALL, **vertical yellow line** anteroposterior axis, **red line** line from outer left to outer right border of ossified ALL, **yellow/green shaded triangle** orientation of midportion of ossified ALL relative to AP axis (°). Experimental DXA scanning techniques: **B** Full exposure scan (FES): maximum amount of ossified ligament present in field of view (**red square**), **white bold arrows** represent DXA scanning orientation. C Parallel scan (PS): minimum amount of ossified ligament present in field of view (**blue square**). **D** Half scan (HS): largest part of ossified ligament is either outside (HSL) or inside (HSR) field of view. Shown here in **yellow** is the HSL.

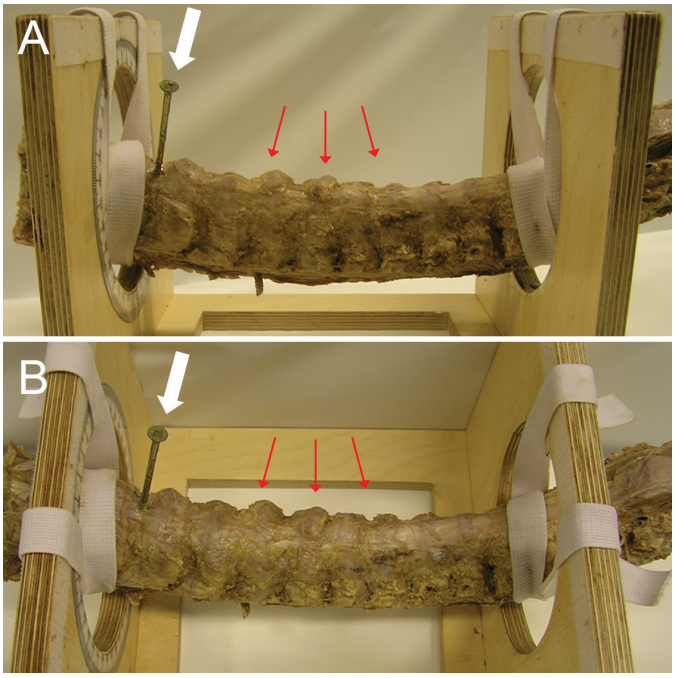

Figure 3
Experimental set-up of a spine affected by DISH fixated in the frame. Correct orientation during DXA scanning was ensured by the protractor on the side of the frame and the pre-drilled screw (**bold white arrow**) in the spine. Note the extensive ossifications in this specimen (**red arrows**). **A** Seen from lateral; **B** Seen from above.

Subsequently, three experimental DXA scans were performed:

1. Scan of the complete vertebrae in the direction perpendicular to the line that can be drawn from the outer left to the outer right border of the ossified ALL, named full exposure scan: **FES** (figure 2B; red square).
2. Scan of the complete vertebrae in the direction perpendicular to the orientation of technique 1, named parallel scan: **PS** (figure 2C; blue square).
3. AP scan of the halves of the vertebrae, named half scan right (**HSR**) and half scan left (**HSL**) (figure 2D; yellow square)

In FES, the maximum amount of ossified ALL was projected in the field of view and should, theoretically, yield the highest BMD possible. In PS, the minimum amount of ossified ligament was projected in the field of view; this orientation should yield the lowest BMD possible. In the HSR scan the largest part of the ossified ligament was *inside* the field of view in DISH specimens, in contrast to the HSL scan where most of the ossified ligament was *outside* the scanning field. Differences in BMD between these latter two scanning orientations should be nonexistent in controls due to the absence of any ossified ligament.

Data analysis and statistics

The contribution of the ossified ligament on the BMD measurements was determined by dividing the BMD of DISH specimens by the BMD of controls multiplied by 100 to get the percentage, followed by subtracting 100% [percentual difference = (BMD DISH/BMD controls) x 100 - 100]. For statistical analysis SPSS software (version 16.0) was used. Differences between the DISH specimens and controls were calculated with a dependent samples t test (significance set at $p < 0.05$).

Results

The mean age at death for donors of the DISH spinal columns was 80.4 ± 8.2 years while for the controls it was 81.0 ± 6.9 years; this difference was not significant ($p = 0.382$). Both groups consisted of five males and five females. The ROI most frequently used for this study were thoracic levels six to nine and seven to ten (table 1).

DISH specimens displayed a statistically significant higher mean BMD than their matched controls in all scanning orientations, except in HSL. In the routine AP view BMD was 0.795 g/cm^2 in DISH specimens (range 0.510 - 1.028 g/cm^2) compared to 0.643 g/cm^2 (range 0.540 - 0.759 g/cm^2) in controls. A normal distribution was observed in these data and there were no outliers. The difference in BMD was most prominent in the FES, where the maximum amount of ossified ALL was present in the field of view; BMD was 0.695 g/cm^2 in DISH specimens compared to 0.514 g/cm^2 in controls (+35.2%). In the PS orientation, where the minimum amount of ossified ligament was present in the scanning field, the difference was considerably smaller; 0.606 g/cm2 vs. 0.469 g/cm2 (+29.2%). See table 2 for more details on the BMD measurements in different DXA scanning orientations. The HSR scan displayed a 39.0% higher BMD in DISH specimens than in controls (0.898 g/cm^2 *vs.* 0.646 g/cm^2). The HSL scans were not significantly different between the groups. The right-left difference was also statistically significant within DISH specimens ($p = 0.001$), but not in controls ($p = 0.825$). See figure 4 for a graphic representation of this finding. Summarizing, all scans incorporating (part of) the ossified anterior longitudinal ligament in the scanning field, yielded higher BMDs than controls.

Table 1
ROIs in ten DISH specimens.

ROI	No. of specimens
T4 – T7	1
T5 – T8	2
T6 – T9	3
T7 – T10	3
T8 – T11	1
Total	**10**

Table 2
Mean BMD of ten DISH specimens vs. ten controls (mean BMD in g/cm^2 ± SEM).

	Controls	DISH	Difference	p-value
AP	0.643 ± 0.027	0.795 ± 0.049	+23.6%	0.004
FES	0.514 ± 0.020	0.695 ± 0.044	+35.2%	0.002
PS	0.469 ± 0.020	0.606 ± 0.042	+29.2%	0.001
HSR	0.646 ± 0.029	0.898 ± 0.059	+39.0%	0.001
HSL	0.643 ± 0.024	0.676 ± 0.046	+5.1%	0.446

AP anteroposterior scan, **FES** full exposure scan, **PS** parallel scan, **HSR** half scan right, **HSL** half scan left

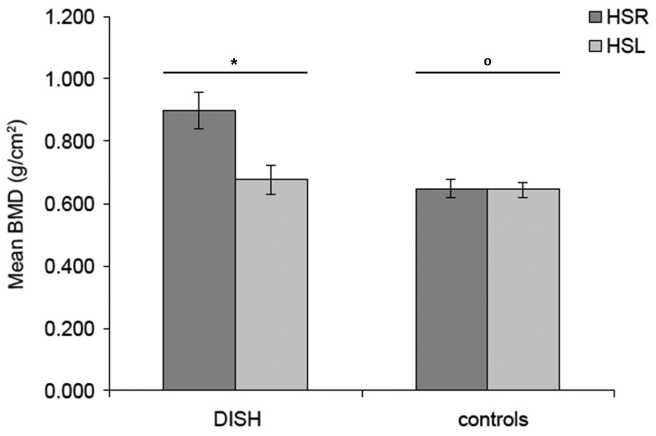

Figure 4
Mean BMD of half scans of ten DISH specimens compared to ten controls. **HSR** half scan right, **HSL** half scan left, * p = 0.001, º p = 0.825.

Discussion

In the present study BMD of ten spinal columns affected by DISH was experimentally investigated and compared to ten age and gender matched non-DISH specimens. It was found that the presence of ossified ligamentous structures in the field of view consistently yielded higher BMDs in DISH specimens, leading to a potential overestimation of BMD ranging from 23.6% to 39.0%. The *vertebral* BMD was not higher in DISH specimens, as demonstrated by comparable BMDs in the HSL scan for both the DISH cases and controls.

As was previously hypothesized, BMD measurements varied for the three experimental scanning orientations. In the DISH specimens differences were most prominent in orientations where the maximum amount of ossified ALL projected in the field of view (FES) and less distinctive in orientations where the minimum amount of ossified ligament was present in the scanning field (PS). Differences were also present in controls, although less profound. It may have been possible that BMD measurements were influenced by the contribution of the posterior elements of the spine during the various scanning orientations, although the exact amount of this contribution is unknown. Because the orientations for the experimental DXA scans were calculated on the two central vertebrae within the ROI of four vertebrae, it may have been possible that ossification of the ALL extended more anteriorly and/or posteriorly at the adjacent levels making it difficult to fully exclude this structure in the PS scan. Overall, the accuracy of positioning the spinal column in the frame may have been higher in the AP and HSL/HSR orientation compared to the other scanning orientations, possibly explaining the large right-left difference in DISH specimens compared to controls. Since all experimental orientations were calculated from the CT data beforehand, using the inserted screw as a reference during CT scanning and for final positioning in the frame before DXA scanning, the influence of this variability on BMD is, however, suggested to be low.

In the present study, BMD was measured in the thoracic spine (T4 – T11), because these regions displayed features of DISH most prominently. Secondly, since the ossified ligament is most asymmetric in the thoracic spine it was feasible to include or exclude this structure during scanning. In clinical practice BMD is usually measured in the lumbar spine (L2 – L4).[11] Although DISH is most commonly encountered in the thoracic spine, ossification of the lumbar spinal ligaments occurs very frequently.[177] In case of lumbar involvement, protruding rather than flowing ossifications are present more often, whereas the asymmetry observed in the thoracic spine is usually not seen, probably due to the more distant (ventral) location of the abdominal aorta from the spine. The overestimation of BMD in the presence of DISH may be different for the lumbar spine but is likely to follow the same mechanism as the thoracic spine and may therefore be substantial.

Other studies concerning BMD in patients with DISH have been published previously. Di Franco *et al.* reported BMD to be increased in the distal radius of 42 DISH patients.[43] Schwartz *et al.* reported high BMD in a patient with exuberant bony changes of the lumbar spine as a result of DISH, whereas BMD of the forearm was decreased.[195] The authors suggested that DISH caused artificially elevated lumbar BMD measured by DXA, but did

not quantify the contribution of the ossified ligament on the BMD measurement. Sahin *et al*. compared the BMD from a group of patients with type 2 diabetes mellitus and DISH to a group of type 2 diabetics without DISH and a group of healthy controls.[186] Both the individuals with DISH and diabetes and the non-DISH diabetics reported a duration of diabetes of approximately ten years. BMD of the lumbar spine was higher in individuals with DISH and diabetes than in diabetics without DISH and the controls. The reported differences in BMD were smaller for the femoral neck and hip. Retrospectively, it may not be unrealistic to suggest that the lumbar spine BMD measurements were artificially increased by the presence of the ossified ligament in the scanning field as demonstrated in the present study.

In conclusion, it was found that in DISH cases the presence of the ossified anterior longitudinal ligament in the scanning field of view consistently led to higher BMDs than in controls. The *vertebral* BMD was comparable in DISH specimens and controls. The results suggest that the presence of DISH may potentially lead to an overestimation of the true vertebral body BMD. Consequently, normal BMD values could imply osteopenia or osteoporosis in patients when features of DISH are present in the scanning field of view. Clinicians should be aware that routine AP spinal measurement of BMD may be unreliable in patients with DISH.

Key messages:

- Presence of DISH in DXA scanning field leads to overestimation of BMD
- Vertebral body BMD is not increased in DISH
- Anteroposterior DXA scanning may be unreliable in DISH patients

CHAPTER 6

Clinical outcome after traumatic spinal fractures in patients with ankylosing spinal disorders compared to control patients

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Submitted for journal publication

Abstract

Background

The clinical outcome after a spinal fracture has been described to be worse in patients with ankylosing spinal disorders (ASD), compared to the general trauma population. In the present study neurological deficits, complications and mortality after spinal injury in patients with ankylosing spondylitis (AS) and diffuse idiopathic skeletal hyperostosis (DISH) were compared to control patients.

Methods

This retrospective cohort study describes patients over 50 years of age and admitted with a traumatic spinal fracture between 2003 and 2009. Data on comorbidity (Charlson score), mechanism of trauma, fracture characteristics, neurological deficit, complications and in-hospital mortality were collected from medical records. With logistic regression analysis the association between the presence of an ASD and mortality was investigated in relation to other known risk factors for mortality.

Results

A total of 156 patients met the inclusion criteria; 14 patients were diagnosed with AS (8.5%), 40 patients had DISH (24.2%) and 111 patients were control patients (67.3%). ASD patients were frequently males and approximately five years older than controls. The Charlson comorbidity score did not significantly differ among the groups, but type 2 diabetes mellitus and obesity were more prevalent among DISH patients. Fractures resulted from low energy trauma and showed a hyperextension configuration in many AS and DISH cases. Patients with AS and DISH were frequently admitted with a neurological deficit, (57.1% and 30.0%, respectively) compared to controls (12.6%, $p = 0.002$), which did not improve in the majority of cases. In AS and DISH patients complication and mortality rates were significantly higher than in controls. Logistic regression analysis showed the parameters age and presence of DISH to be independently, statistically significantly related to mortality.

Conclusions

Many patients with AS and DISH showed unstable (hyperextension) fracture configurations frequently associated with a neurological deficit. Complication and mortality rates were higher in patients with ASD compared to control patients. Increasing age and presence of DISH are predictors of mortality after a spinal fracture.

Introduction

Progressive ankylosis of the spine is a hallmark of two distinct diseases; ankylosing spondylitis (AS) and diffuse idiopathic skeletal hyperostosis (DISH). AS is an inflammatory disease associated with the HLA B-27 gene. Chronic inflammation of the sacroiliac joints, intervertebral discs and facet joints eventually leads to complete ankylosis of the spinal column. Typically, the disease starts in adolescence and predominantly affects males in a male:female ratio of 3:1. The prevalence of AS is relatively stable and ranges between 0.1% and 1.4%.[21] Several authors have reported AS patients to have a three to fourfold risk of spinal fractures during their lifetime, increasing with duration of the disease.[57;59] Neurological deficits as a result of unstable spinal fractures are well known and notorious complications of longstanding AS.[151] Although an increasing amount of evidence suggests that patients with spinal ankylosis due to DISH are also at risk for unstable fractures of the spine (figure 1), the awareness for DISH is much lower among clinicians.[128;197] DISH is considered to be a non-inflammatory systemic condition that leads to ossification of ligaments and entheses, predominantly in the spinal column. The diagnosis DISH is established when flowing ossification over at least four contiguous vertebrae is present on conventional radiographs with sparing of the intervertebral disc space.[178] Its etiology is currently unknown, yet several authors have described associations with advancing age, obesity and type 2 diabetes mellitus.[41;108] DISH also shows a male predominance (in a ratio of 3:2) and is rarely seen before the age of 50.[235] The prevalence has been reported to range from 2.9% in a Korean population to 25% in Caucasian males in the USA and is likely to increase because of its association with obesity and diabetes; conditions that rapidly become endemic in urbanized societies.[106;234] Physicians should, therefore, expect to admit increasing numbers of patients with DISH and spinal fractures.

Figure 1
Hyperextension fracture in spine with 'flowing wax' ossification typical for DISH.

Because ankylosing spinal disorders (ASD) are often associated with pre-existing back pain of varying intensity, diagnosing spinal fractures can present a major challenge for physicians; especially since these fractures occur frequently after trivial trauma.[90] Furthermore, pre-existent abnormalities on spine radiographs may mask or obscure minimally displaced fractures.[40] Patients with fractures of the ankylosed spine often present with spinal cord injury (SCI) due to gross displacement of the spinal canal.4 Some patients, however, do not experience any neurological deficit until a sudden deterioration occurs (this interval has aptly been described the 'fatal pause').[48] Secondary worsening of neurological status may also occur due to inadequate immobilization, unwarranted transfers or imprudent manipulation of this group of patients.[165;223] Lastly, patients with ASD and spinal fractures may display higher complication and mortality rates compared to non-ankylosed spine trauma victims.[193;236] Despite numerous case series and literature reviews, comparative cohort studies on the outcome and survival of patients with ASD sustaining a spinal fracture are absent. As a result, it remains unclear what exactly causes the poor outcome in this apparently vulnerable patient category. The primary purpose of the present cohort study was to compare neurological deficits, complications and mortality after a traumatic spine fracture, in patients with ankylosing spinal disorders (AS and DISH) and non-ankylosed trauma patients. In addition, we investigated the association between ASD and mortality in relation to known risk factors influencing the outcome of trauma patients including age, comorbidity, severity of injury and presence of neurological deficit.[85;144]

Methods

Patient sample

This retrospective cohort study describes patients with traumatic spinal fractures admitted to our institution, a regional level-1 trauma center and tertiary referral spine center. Combining the databases of the Emergency Department and Department of Orthopedics assured identification and inclusion of all patients eligible for this study. Inclusion criteria were: patients over 50 years of age with a traumatic fracture of the spine (cervical/thoracic/lumbar) and admission date between January 1st 2003 and December 31st 2009. The minimum age criterion was imposed because ankylosing disorders of the spine are rare occurrences in younger individuals.[57;177] Exclusion criteria were: isolated spinous process or transverse process fractures or exclusive ligamentous injury. Upon identification of all patients with traumatic spine fractures, the electronic medical record, radiographic examinations and reports were reviewed to identify individuals with ASD. All relevant conventional radiographs, computed tomography (CT) and magnetic resonance images (MRI) available were reviewed by two authors to establish the diagnosis AS or DISH, record fracture level(s), deduct fracture mechanism and classify the fracture. When consensus on the diagnosis or fracture characteristics could not be reached, a third observer was consulted.

Table 1
Parameters extracted from (hard copy) medical records.

Parameter	Definition
Gender	Male or female
Age at time of injury	Years
Transfer	Transfer from other hospital
Delayed diagnoses	Diagnosis established > 24 hours after trauma
Patient's delay	Patient delayed to seek medical attention
Doctor's delay	Physician failed to timely recognize fracture
Traumatic impact	High energy trauma (HET): high speed MVA or fall > 15 feet[6] Low energy trauma (LET): fall from standing or sitting position
Number of fractures	
Fracture level	C0-C2, C3-C7, T1-T12, L1-L5
Fracture classification	
C0-C2	Atlas fractures classified according to Levine and Edwards[119], fractures of the odontoid process according to Anderson & D'Alonzo[8] and fractures of the odontoid body according to Levine and Edwards[120]
C3-L5	Fractures classified according to an algorithm derived from the AO Spine fracture classification; A = compression (posterior ligamentous complex (PLC) intact), B *flexion* = flexion/distraction (B.1 and B.2, PLC disrupted), B *extension* = hyperextension (B.3), C = shear/rotation[133]
Polytrauma	Injury to at least two body regions with abbreviated injury scale (AIS) ≥ 3, with the presence of systemic inflammatory response syndrome (SIRS) on at least one day during the first 72 hours[26]
Hospital stay	Duration of hospital stay (days)
Comorbidities	According to the Charlson Comorbidity Index; a validated score predicting cumulative increased likelihood of one-year mortality[208]
Obesity	Body mass index (BMI) > 30 or notion of obesity in physical exam description
Presence of ASD	AS according to the modified New York criteria[227]; DISH according to criteria of Resnick & Niyawama[178]
Treatment strategy	Surgical treatment: posterior long segment fixation (> three vertebrae), posterior short segment fixation (three vertebrae), anterior fixation, combined anterior & posterior fixation, vertebroplasty, laminectomy and percutaneous posterior fixation Conservative treatment: halo traction, halo immobilization, collar, brace, plaster jacket, bed rest, admittance to intensive care unit and no immobilization
Timing of surgery	Number of days between admission and surgery (days)
Surgical duration	Duration of surgical procedure (hours)
Blood loss	Blood loss during surgery (milliliters)
Immobilization type	Halo traction, halo immobilization, collar, brace, plaster jacket, bed rest, admittance to intensive care unit and no immobilization
Immobilization duration	Duration of immobilization (days)
Neurological status	According to ASIA impairment scale (at admission, discharge and follow up)[7]
Follow up	Outpatient examinations at six weeks, three months, six months and one year; follow up data were included if at least one outpatient examination was recorded
Complications	Instrumentation failure (*e.g.* migration or loosening of screws/rods), wound infection, complications of halo frame (*e.g.* pin site infection, pin loosening/migration), respiratory failure, pneumonia, pneumothorax, delirium, decubitus ulcer, atrial fibrillation, urinary tract infection, sepsis, dysphagia, ileus, progressive kyphosis, pseudo arthrosis, chronic pain, miscellaneous complications
Mortality	Number of patients deceased during hospitalization

Baseline parameters

For each patient predefined and generally accepted parameters (listed in table 1) were extracted from the patient's electronic and hard copy medical record. Patients with more than one fracture were included in the analyses once; their fracture level was assigned either to the fracture level that corresponded to the level of SCI or to the fracture level dictating treatment strategy in the absence of neurological deficits.

Statistical analysis

SPSS version 16.0 was used for statistical analysis. For categorical variables of baseline parameters X^2 or Fisher exact test (if cell size < 5) was used; for continuous variables one-way ANOVA was used. To assess the influence of each proposed risk factor on the mortality the odds ratio (with 95% confidence interval) was determined with univariable logistic regression analysis. These risk factors were: gender, age, Charlson score for comorbidities, presence of AS, presence of DISH, presence of low energy trauma, presence of polytrauma, presence of delayed diagnosis, occurrence of complication(s) and neurological deficit according to the ASIA impairment scale. Risk factors with a p-value < 0.20 or of clinical interest were subsequently analyzed in the multivariable logistic regression model. Significance was set at $p < 0.05$ in all other analyses.

Results

Patient sample

A total of 556 patients with traumatic spinal fractures were admitted at our institution in the inclusion interval. From this cohort a total of 165 patients met the inclusion criteria and were included in the present study. Fourteen patients were diagnosed with AS (8.5%) and 40 patients had DISH (24.2%); the remaining 111 patients (67.3%) showed no features of ASD and were assigned to the control group.

Baseline parameters

The proportion of males ranged from 60.0% in the control group to 85.7% in AS patients. The mean age was higher in patients with ASD; 69.5 ± 9.9 years in AS patients and 68.4 ± 10.0 years in DISH patients, compared to 64.4 ± 10.7 years in controls ($p = 0.046$). Low energy trauma caused fractures in nine AS patients (64.3%), in three DISH patients (32.5%) and 28 control patients (25.2%); this difference was significant ($p = 0.014$). Two patients with AS (14.3%) were polytrauma patients, *vs.* 14 DISH patients (35.0%) and 43 controls (38.7%). The diagnosis was delayed in 19 patients (11.5%); in four AS patients (28.6%), in seven DISH patients (17.5%) and eight controls (7.2%) ($p = 0.019$). Patient's delay occurred in three AS patients (21.4%), five DISH patients (12.5%) and eight controls (7.2%). Doctor's delay occurred in one AS patient (7.1%) and two DISH patients (5.0%), this type of delay was not found in control patients ($p = 0.047$). Ten AS patients (71.4%) were transferred to our institution from another hospital, this was also the case for 17 DISH patients (42.5%) and 34 control patients (30.6%); this finding was

Table 2
Baseline characteristics of the study population.

	AS	DISH	Controls	p-value
Number of patients (% male)	14 (85.7)	40 (70.0)	111 (60.4)	0.129
Mean age	69.5 ± 9.9	68.4 ± 10.0	64.4 ± 10.7	**0.046**
Low Energy Trauma (%)	9 (64.3)	13 (32.5)	28 (25.2)	**0.014**
Mean number of fractures	1.6 ± 0.3	1.8 ± 1.0	1.6 ± 0.9	0.570
Polytrauma patients (%)	2 (14.3)	14 (35.0)	43 (38.7)	0.206
Delayed diagnosis (%)	4 (28.6)	7 (17.5)	8 (7.2)	**0.019**
Doctor's delay (%)	1 (7.1)	2 (5.0)	0	**0.047**
Patient's delay (%)	3 (21.4)	5 (12.5)	8 (7.2)	0.122
Transfer from hospital (%)	10 (71.4)	17 (42.5)	34 (30.6)	**0.010**
Surgical treatment (%)	8 (57.1)	21 (52.5)	39 (35.8)	0.072
Timing of surgery (days)	5.0 ± 5.1	2.7 ± 3.5	2.1 ± 4.0	0.185
Surgical duration (h)[1]	4:24 ± 1:23	3:23 ± 0:54	3:40 ± 1:18	0.140
Blood loss during surgery (ml)[2]	960 ± 532	788 ± 855	613 ± 681	0.543
Mean hospital stay (days)	21.0 ± 21.5	29.4 ± 37.6	22.7 ± 28.3	0.455
Mean follow up (months)[3]	9.1 ± 8.1	11.8 ± 9.6	12.2 ± 8.8	0.684
Mean Charlson score (range)[4]	1.0 ± 1.2	1.3 ± 1.4	0.9 ± 1.2	0.156
Cardiovascular disease (%)	3 (21.4)	9 (23.1)	26 (23.6)	1.000
Pulmonary disease (%)	1 (7.1)	9 (23.1)	16 (14.5)	0.331
Diabetes mellitus (%)	2 (14.3)	12 (30.8)	11 (10.0)	**0.007**
Neuromuscular disease (%)	3 (21.4)	4 (10.3)	7 (6.4)	0.110
Renal disease (%)	1 (7.1)	0	2 (1.8)	0.365
Liver disease (%)	0	3 (7.7)	1 (0.9)	0.080
Malignancy (%)	0	5 (12.8)	10 (9.1)	0.413
Obesity (%)[5]	4 (33.3)	13 (50.0)	8 (12.9)	**0.001**

All results are based on the total study group (165 patients) except for: [1]based on 67 patients, [2]based on 45 patients, [3]based on 125 patients, [4]based on 163 patients, [5]based on 100 patients.

significant too (p = 0.010). The mean Charlson score was 1.0 in AS patients; 1.3 in DISH patients and 0.9 in the control group (p = 0.156). Comorbidities frequently reported in all patient categories were cardiovascular disease, pulmonary disease and type 2 diabetes mellitus. Diabetes was more frequently diagnosed in the DISH group compared to the AS and control groups (in 30.8% *vs.* 14.3% and 10.0% of patients, respectively; p = 0.007), as was obesity, which was observed in 50.0% of DISH patients, 33.3% of AS patients and 12.9% of control patients (p = 0.001). The remaining comorbidities did not statistically differ between the groups. See table 2 for more details on the baseline characteristics of the study population. In patients with DISH, flowing ossifications were most frequently observed in the mid-thoracic spine with relative sparing of the cervicothoracic junction and lumbar spine. In patients with AS the ossifications were distributed evenly at all levels (figure 2).

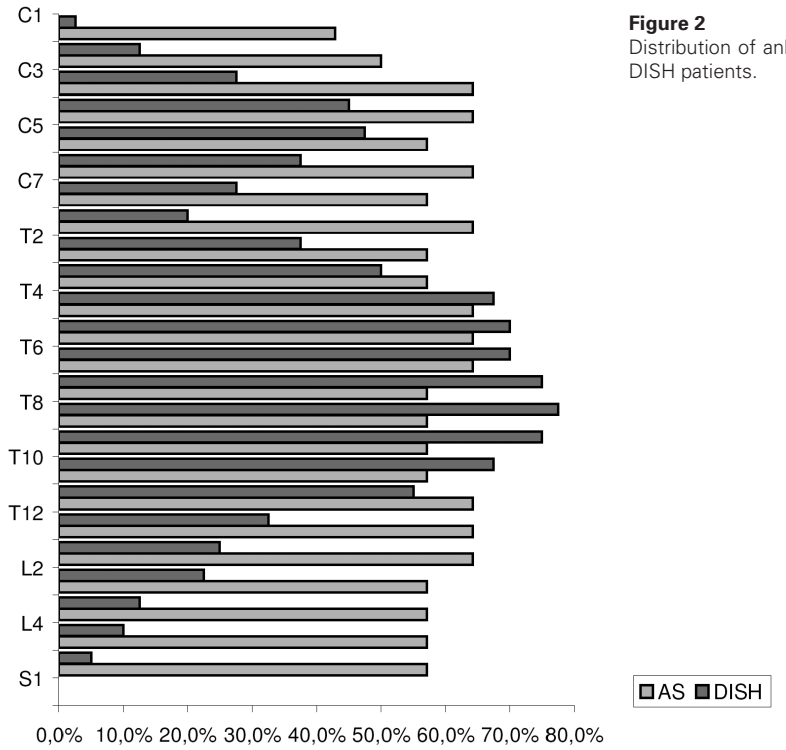

Figure 2
Distribution of ankylosis in AS and DISH patients.

Fracture characteristics

A total of 275 fractures were recorded in 165 patients. The fracture dictating the treatment strategy was localized at the level of C1-C2 in seven DISH patients (17.5%) and 26 controls (23.4%), but in no AS patients. Among these fractures were type 2 and 3 odontoid fractures, Hangman's fractures and lamina fractures or a combination of these fracture types. The subaxial spine was frequently affected in AS patients; in eight AS patients (57.1%), 14 DISH patients (35.0%) and 23 control patients (20.7%) the fractures were localized at C3-C7. Bilateral facet joint dislocations were observed in five DISH patients (12.5%) and six controls (5.4%). Fractures were localized in the thoracic spine in two AS patients (14.3%), 11 DISH patients (27.5%) and 31 control patients (27.9%). In four AS patients (28.6%), eight DISH patients (20.0%) and 31 control patients (27.9%) the fracture was localized in the lumbar spine ($p = 0.057$) (table 3).

Classification of the fractures showed type A (compression) fractures to occur mainly in control patients; in 37 controls (43.5%) a compressive force caused the fracture, compared to one AS patient (7.1%) and five DISH patients (15.2%). Type B *flexion* fractures were observed in four AS patients (28.6%), in 11 DISH patients (33.3%) and in 35 control patients (41.2%). Interestingly, type B *extension* fractures were the most common fractures in AS and DISH patients (64.3% and 45.5%, respectively) but were less common in controls (11.8%). Type C fractures were rarely seen in any patients; two DISH patients

(6.1%) and three control patients (3.5%) showed a shear/rotation fracture configuration. The differences in fracture configuration between the groups were highly significant ($p < 0.001$). See table 4 for more details.

Treatment strategy

Surgical treatment was performed in eight AS patients (57.1%), 21 DISH patients (52.5%) and 39 control patients (35.8%) for a total of 68 patients. Surgery was performed on average 5.0 ± 5.1 days after trauma in AS patients, compared to 2.7 ± 3.5 days in DISH patients and 2.1± 4.0 days in controls ($p = 0.185$); no significant differences were observed in surgical duration or blood loss during surgery either (table 2). Posterior long segment fixation was performed most frequently in patients with AS and DISH, whereas posterior short segment fixation was the treatment of choice in control patients. Posterior stabilization was combined with decompressive laminectomy when a neurological deficit was present or when substantial intraoperative reduction maneuvers were anticipated. In nine control patients and five DISH patients, pedicle screw fixation was performed percutaneously (see figure 3).

Ninety-five patients were treated conservatively; comprising of 70 controls (64.2%), six AS patients (42.9%) and 19 DISH patients (47.5%). The mean immobilization duration was 58.9 ± 29.4 days in control patients, 53.8 ± 64.6 days in AS patients, and 61.7 ± 55.1 days in DISH patients ($p = 0.906$). In case of cervical fractures, halo immobilization was most frequently performed; thoracic and lumbar fractures were treated with plaster jackets.

Table 3

Fracture localization in AS, DISH and control patients, number of patients (%).

	AS	DISH	Controls	Total	p-value
C1-C2	0	7 (17.5)	26 (23.4)	33 (20.0)	
C3-C7	8 (57.1)	14 (35.0)	23 (20.7)	**45 (27.3)**	
T1-T12	2 (14.3)	11 (27.5)	31 (27.9)	**44 (26.7)**	
L1-L5	4 (28.6)	8 (20.0)	31 (27.9)	43 (26.1)	
Total	**14**	**40**	**111**	**165**	**0.057**

Table 4

Fracture mechanism according to the AO classification, number of patients (%).

	AS	DISH	Controls	Total	p-value
Type A	1 (7.1)	5 (15.2)	37 (43.5)	43 (32.6)	
Type B *flexion*	4 (28.6)	11 (33.3)	35 (41.2)	50 (37.9)	
Type B *extension*	9 (64.3)	15 (45.5)	10 (11.8)	34 (25.8)	
Type C	0	2 (6.1)	3 (3.5)	5 (3.8)	
Total	**14**	**33**	**85**	**132**	**0.000**

Based on 132 fractures C3-L5

Eleven patients received bed rest as primary treatment strategy including nine patients who were admitted at an intensive care unit (ICU) for concomitant injuries. See figure 4 for more details on conservative treatment.

Neurological function

Neurological function could be assessed in 154 patients at the time of admission; an initial ASIA score could not be determined in 11 patients since these patients were unconscious at initial admission. Significantly more patients with ASD displayed a neurologic deficit (ASIA A-D); in eight AS patients (57.1%) and 12 DISH patients (30.0%) neurological function was impaired, compared to 14 controls (12.6%; p = 0.002).

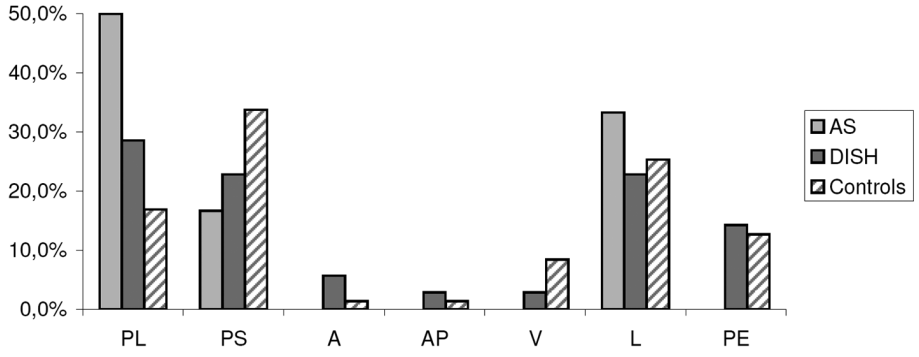

Figure 3
Treatment strategies in 68 surgically treated patients.
PL posterior long segment fixation (>3 consecutive levels), **PS** posterior short segment fixation (3 levels), **A** anterior fixation, **AP** combined anterior & posterior fixation, **V** vertebroplasty, **L** laminectomy, **PE** percutaneous. Note: since surgical strategies could be combined, total > n = 68.

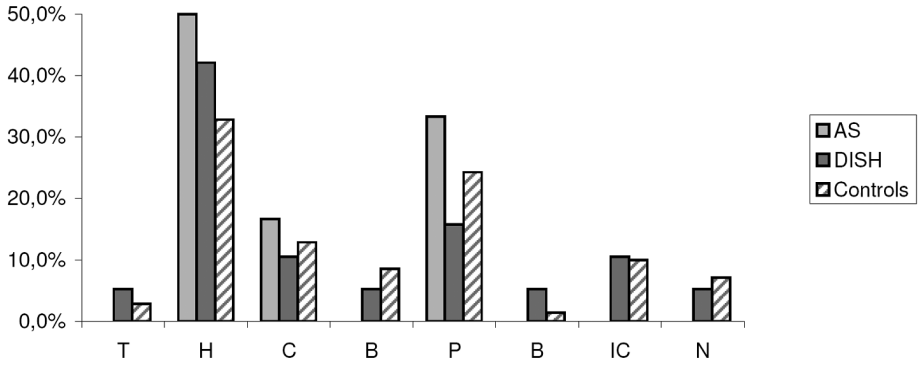

Figure 4
Treatment strategies in 95 conservatively treated patients.
T halo traction, **H** halo immobilization, **C** collar, **B** brace, **P** plaster jacket, **B** bed rest, **IC** intensive care unit admittance (bed rest), **N** no immobilization.

The majority of these patients had unchanged neurological status post-treatment (surgical or conservative); in 6 AS patients (42,9%), 10 DISH patients (25,0%) and 11 control patients (9,9%) with neurological impairment (ASIA A-D) at admission no alteration in motor and sensory function was observed during hospitalization. Improvement of neurological function was observed in seven patients in total (4.2%); two AS patients (14.3%), two DISH patients (5.0%) and three control patients (2.7%) improved one ASIA grade. Deterioration of neurological function was observed in five patients in total (3.0%); in one AS patient (7.1%) and in four control patients (3.6%). See table 5 for more details on the neurological status of this study cohort.

Table 5

Neurological status of AS, DISH and control patients at admission, discharge and follow up.

		Admission n = 165			**Discharge n = 163**			**Follow up n = 125**
	ASIA	n (%)	↑	↓	n (%)	↑	↓	n (%)
AS	A	3 (21.4)			3 (21.4)			
	B							2 (28.6)
	C							
	D	5 (35.7)	2 E (1 ST)		4 (28.6)			
	E	6 (42.9)		1 D	7 (50.0)			5 (71.4)
DISH	A	3 (7.5)			3 (7.5)			1 (3.8)
	B	3 (7.5)	2 C (ST)		1 (2.5)	1 C (ST)		
	C				2 (5.0)			3 (11.5)
	D	6 (15.0)			6 (15.0)	1 E (ST)		3 (11.5)
	E	25 (62.5)		2 other[1]	24 (60.0)			18 (69.2)
	Other				2 (5.0)	1 E		1 (3.8)
	Low EMV	3 (7.5)	1 E (ST)		2 (5.0)			
Controls	A	1 (0.9)			3 (2.8)	1 B (ST)		1 (1.1)
	B	1 (0.9)	2 D (ST)		2 (1.8)	1 D (ST)		1 (1.1)
	C	2 (1.8)	1 E (ST)		1 (0.9)	1 D (ST)		
	D	10 (9.0)		1 B (ST)[2]	12 (11.0)	1 E (ST)		9 (9.8)
	E	89 (80.2)	2 D (1 ST)	2 A (ST)[3] 1 C (ST)[4]	90 (82.6)			81 (88.0)
	Low EMV	8 (7.2)	3 E (2 ST)	2 †	1 (0.9)			

↑ improvement of neurological function, ↓ deterioration of neurological function, **ST** surgical treatment, otherwise conservative treatment was performed, **low EMV** neurological status could not be verified because of EMV < 3 at admission, **†** two patients died without treatment being administered, because of infaust prognosis.[1] Hemiplegia after cerebrovascular infarction in one patient; hemiplegia resulting from neurotrauma in the other patient.[2] Deterioration of neurological function after flexion-extension radiography with unidentified fracture. [3] Severe deterioration of neurological function following epidural analgesia administration with unidentified fracture in one patient; in the other patient exact onset of neurological deficit was unclear; at admission normal function was recorded. [4] Underestimated severe discoligamental injury.

Complications

Irrespective of treatment strategy, the complication rates were higher in patients with ASD than in control patients. In the surgical group seven AS patients (87.5%) and 18 DISH patients (85.7%) had one or more complication(s). In comparison, 19 control patients (48.7%) sustained complications (p = 0.006). Complications reported most frequently involved the respiratory tract (respiratory failure, pneumonia), although delirium, decubitus and atrial fibrillation were also common. Complications related to the surgical procedure, such as instrumentation failure or wound infection, were reported in four AS patients (50.0%), three DISH patients (14.3%) and 11 control patients (28.5%). See table 6 for more details on complications.

In the conservatively treated patients six AS patients (100.0%), 13 DISH patients (68.4%) and 27 controls (38.6%) suffered complications, predominantly consisting of pneumonia and respiratory failure (p = 0.001).

Table 6

Complications in surgically and conservativerly treated patients.

	AS		**DISH**		**Controls**		**Total**
	ST	**CT**	**ST**	**CT**	**ST**	**CT**	
Instrumentation failure	3		1		4		**8**
Wound infection	1		2		7		**10**
Halo complications	1			3		2	**6**
Respiratory failure	2	1	7	5	7	10	**32**
Pneumonia	2	1	7	4	7	8	**29**
Tracheostomy	1	1	3		7	6	**18**
Pneumothorax					1	5	**6**
Delirium	3		8	3	2	6	**22**
Decubitus ulcer	2	1	6		3	3	**15**
Atrial fibrillation	1		1	2	3	3	**10**
Urinary tract infection	1				2	2	**5**
Suprabupic catheter	1		1		4		**6**
Sepsis	1		2		1		**4**
Dysphagia			4		2	1	**7**
Gastrostomy			2		2	1	**5**
Ileus					4		**4**
Miscellaneous complications		1	1	1	1	2	**6**
Total reported	19	5	45	18	57	49	**193**

ST surgical treatment, **CT** conservative treatment. Miscellaneous complications: complications observed once (exacerbation COPD, deep venous thrombosis, peptic ulcer, meningitis), or twice (depressive disorder) in the entire population. * Recorded at follow up. Note: patients could sustain multiple complications, therefore number of complications > number of patients.

Six out of 37 patients (16.2%) treated with halo traction or halo immobilization experienced complications associated with the fixation device, such as pin loosening or pin tract infection.
In 13 patients initially receiving nonoperative care, treatment was eventually converted to surgery. Progressive neurological deficit was the reason to convert in five patients, whereas eight patients were operated because of inadequate reduction and/or insufficient stability. Clinical details of these patients are presented in table 7.

Mortality

Overall mortality was 6.1% in this cohort; one AS patients (7.1%), six DISH patients (15.0%) and three control patients (2.7%) died during hospitalization; this difference between patient groups was statistically significant (p = 0.015). The cause of death was respiratory failure in four patients. Three patients died of the consequences of neurotrauma, neurogenic shock and cerebrovascular accident, respectively. Three other patients were determined brain dead after successful resuscitation following out-of-hospital cardiac arrest and life-support measures were subsequently discontinued. See table 8 for more details on mortality within the patient groups.

Risk factors for mortality

Univariable logistic regression analysis showed the parameters age (odds ratio 1.14, 95% CI 1.06 – 1.23), the presence of DISH (odds ratio 5.34, 95% CI 1.42 – 20.01) and neurological deficit to be associated with mortality. With respect to the categorical parameter of the ASIA impairment scale the model showed that the effect of gradation ASIA A was significantly different from gradation ASIA E (odds ratio 29.25, 95% CI 4.44 – 192.70, p = 0.000); whereas the other grades (ASIA B, C and D) did not show a significant difference from ASIA E (table 9).
The combination of these parameters in the multivariable logistic regression analysis showed that age and presence of DISH were still significantly related to mortality, however, the ASIA grade was no longer significantly related with mortality (p = 0.123). The odds ratio for age was 1.21 (95% CI 1.04 – 1.40, p = 0.015) and the odds ratio for DISH was 15.75 (95% CI 1.26 – 196.47, p = 0.032). These results indicate that patients with DISH have a higher odds of death after sustaining spinal fracture, increasing further with age.

Outcome at follow up

Most patients showed no alteration in neurological status at follow up; out of 125 patients whose follow up data were available for analysis, neurological improvement was observed in three out of 26 DISH patients (11.5%) and four out of 92 controls (4.3%). Most patients improved one ASIA grade; one control patient showed improvement of two grades; from ASIA B to D (see table 5 for more details).
After surgical treatment (56 in total) two out of six AS patients (33.3%), six out of 16 DISH patients (37.5%) and 13 out of 34 control patients (38.2%) reported chronic pain at follow up. Pseudo-arthrosis was recorded in one control patient (2.9%) and progressive kyphosis in one DISH patient (6.2%) and two control patients (5.9%). Among conservatively treated

patients (69 in total) chronic pain was reported by five out of ten DISH patients (50%) and 23 out of 58 control patients (39.7%). Pseudo-arthrosis was observed in three controls (5.2%) and progressive kyphosis in one DISH patient (10.0%) and 11 controls (19.0%). No hazards were recorded in the AS patient in this group. There were no statistically significant differences between the patient groups in these parameters.

Discussion

In this retrospective cohort study of patients with traumatic spinal fractures we found the rates for mortality, neurological deficit and complications to be significantly higher in patients with spinal ankylosis than in control patients. With respect to demographic data pertaining to patients with ASD, we were able to confirm previous findings.[32;193] The percentage of male patients was higher in AS and DISH than in control patients and patients with ASD were approximately five years older than controls. Type 2 diabetes

Table 7

Conversion of treatment in 11 conservatively treated patients.

Gender, age	History	ASD	CS	Fracture level (type/AO-class)	ASIA admission	Treatment, days	ASIA treatment
M, 74	LET, fall	AS	1	C6	D	C, 29	D
M, 61	HET, fall		1	C6-C7 (BFD)	B	T, 3	B
F, 72	HET, fall		1	L3 (A)	E	P, 29	E + RC
M, 56	HET, fall		0	C5-C6	D (CCL)	T, 5	D (CCL)
M, 52	LET, fall	DISH	2	T12 (A)	E	P, 210	E
M, 62	HET, fall	DISH	0	C7-T1 (BFD)	E	T, 5	E
F, 75	LET, fall	AS	2	L1 (Bext)	E	P, 1	D
F, 67	LET, fall	DISH	3	C2 (O type 3)	E	H, 138	E
M, 50	LET, fall		7	C5-C6 (BFD)	D (CCL)	H, 84	D (CCL)
F, 61	HET, MVA		0	C2 (O type 3) & T12-L1	E (polytrauma)	H, 3	E
M, 67	LET, fall	AS	1	C5-C6	D	H, 68	D
M, 54	HET, fall	AS	0	C7	D	H, 176	E
M, 57	HET, fall	DISH	0	C6	E	C, 124	E + RC

M male, **F** female, **LET** low energy trauma, **HET** high energy trauma, **MVA** motor vehicle accident, **ASD** ankylosing spinal disorder, **AS** ankylosing spondylitis, **DISH** diffuse idiopathic skeletal hyperostosis, **CS** Charlson score, **BFD** bilateral facet dislocation, **O** odontoid, **CCL** central cord lesion, **RC** root compression, **T** halo traction, **H** halo immobilization, **C** collar, **P** plaster jacket, **PND** progressive neurologic deficit (*after discharge), **IR** inadequate reposition, **PPK** pain + progressive kyphosis, **PPA** pain + pseudo arthrosis, **UF** unstable fracture, **PL** posterior long segment fixation, **L** laminectomy, **PS** posterior short segment fixation, **A** anterior fixation, **V** vertebroplasty, **NR** not recorded-, **NI** no immobilization, **D** delirium, **P** pneumonia, **RF** respiratory failure, **T** tracheostomy, **U** urinary tract infection, **DV** deep venous thrombosis, **DY** dysphagia, **DE** decubitus ulcer, **WI** wound infection, **PE** pulmonary embolus.

mellitus and obesity were more frequently reported in DISH patients, compared to AS and control patients. Establishing a timely diagnosis and treatment plan was more difficult in patients with ASD, as can be concluded from the results pointing to a difference in doctor's delay between the ASD and control groups. Fractures in patients with ASD often resulted from trivial trauma, for example falls from a standing or sitting position, possibly causing some physicians to underestimate the injury severity. Difficult interpretation of radiological examinations showing gross pathological changes to the spine could also be responsible for this phenomenon.[213] Many patients with AS (71.4%) and DISH (42.5%) were referrals from other hospitals (controls 30.6%), resulting in a longer period of time elapsed between fracture diagnosis and definitive treatment in this category of patients.

The fracture configuration in patients with ASD often differs from trauma patients without spinal ankylosis. Hyperextension fractures are relatively rare occurrences in the 'general' spine trauma population; Magerl and coworkers calculated the percentage of this type of fracture at 0.2% in their study of 1445 spine fractures.[133] In the present work type B

Table 7

Continued

Rationale surgery	Surgery	Levels	Duration (h)	Blood loss (ml)	Immobilization, days	ASIA discharge	Complications
PND*	PL + L	C4-C7	3:00	NR	H, 42	D	D
IR	PS	C6-C7	3:00	1600	H, 42	B	P,RF,T,U,DV,DY,DE
PND	PS + L	L2-L4	3:53	1000	P, 42	E	WI
IR	A	C5-C6	2:59	50	H, 84	E	-
PPK	V	T12	1:20	NR	-	E	-
IR	PS	C7-T1	2:00	950	H, 42	E	WI
PND	PL + L	T11-L3	3:49	2300	-	D	WI
PPA	PS	C1-C2	4:53	400	-	E	RF
PND	A	C5-C6	2:58	150	-	D	-
UF	A	C2	2:00	NR	H, 42	D	-
UF	PL + L	C3-C7	3:16	300	H, 14	D	-
UF	PL + L	C3-T3	3:37	1400	H, 70	E	-
PND	PS	C6-C7	5:06	400	-	E	WI, P, PE

Table 8

Mortality of AS, DISH and control patients.

		AS	DISH	Controls	p-value
ST	Neurotrauma		1 (0 days)		
	Neurogenic shock		1 (5 days)		
CT	Respiratory failure	1 (7 days)	2 (9 & 12 days)	1 (1 day)	
	Cerebrovascular accident		1 (0 days)		
	Out-of-hospital cardiac arrest		1 (2 days)		
	Withdrawn from treatment*			2 (1 day)	
Total (%)		**1 (7.1)**	**6 (15.0)**	**3 (2.7)**	**0.015**

ST surgical treatment, **CT** conservative treatment. * These two patients were determined brain dead after resuscitation following out-of-hospital cardiac arrest; because of infaust prognosis no treatment was administered

Table 9

Univariable and multivariable logistoc regression analysis of risk factors associated with mortality.

Risk factors	Univariable			Multivariable		
	Odds	95% CI	p-value	Odds	95% CI	p-value
Gender	0.52	0.14 – 1.88	0.317			
Age	1.14	1.06 – 1.23	0.001	1.21	1.04 – 1.40	0.015
Charlson comorbidity index	1.15	0.72 – 1.83	0.562			
AS	1.21	0.14 – 10.34	0.859			
DISH	5.34	1.42 – 20.01	0.013	15.75	1.26 – 196.47	0.032
LET	0.56	0.11 – 2.72	0.470			
Polytrauma	0.19	0.02 – 1.51	0.115			
Delayed diagnosis	0.85	0.10 – 7.07	0.877			
Complication	$1.56 * 10^8$	0.00 – .	0.997			
ASIA impairment scale			0.015			0.123
ASIA A	29.25	4.44 – 192.70	0.000			
ASIA B	0.00	0.00 – .	0.999			
ASIA C	0.00	0.00 – .	1.000			
ASIA D	0.00	0.00 – .	0.998			
ASIA E (reference)	1					

extension fractures accounted for 64.3% and 45.5% in the AS and DISH groups, respectively. It has previously been hypothesized that a traumatic impact that would normally not lead to fracture in a flexible spine, can result in fracture in the ASD-affected spine.[40;73] Advanced ankylosis may lead to long lever arms on which traumatic forces can act, resulting in hyperextension fractures after a simple backward fall or low-velocity rear-impact motor vehicle accident.[25] Moreover, since stabilizing soft tissues (joint capsules and ligaments) are also involved in the ossifying processes of both AS and DISH, fractures in ASD typically propagate through all three columns and tend to result in highly unstable and displaced fracture configurations, similar to long bone fractures in extremities.

Many patients with AS or DISH were admitted with a neurological deficit associated with the injury sustained (57.1% and 30.0%, respectively). This unusually high percentage could be directly related to the unstable nature and propensity of this type of fracture to displace. The neurological status did, unfortunately, not improve in the majority of patients regardless of treatment initiated, which may have been related to a delay in treatment in some cases. Some patients improved one ASIA grade while only one patient improved two ASIA grades, observations consistent with the study of Caron *et al.*, in which the clinical outcomes of patients with DISH and AS with a spinal fracture were compared.[32] In 12.6% of the control patients from this cohort a neurological deficit was present. This percentage is considerably higher than quoted normally from the literature and probably reflects a referral bias.[228] Complication and mortality rates were significantly increased in patients with ASD compared to controls. After operative treatment 87.5% of AS patients and 85.7% of DISH patients had at least one complication, following nonoperative treatment these percentages were 100% and 68.4%, respectively. These numbers are comparable to the study of Caron *et al.*, in which 84% of patients with ASD were reported to have one or more complications.[32]

In-hospital mortality was significantly higher among patients with ASD than in control patients in this cohort; 7.1% of AS patients, 15.0% of DISH patients and 2.7% of controls died during hospitalization. Caron and coworkers reported an overall mortality of 32% in their cohort; 21.1% of AS patients and 38% of DISH patients died within the follow-up period (6.5 months).[32] The prevalence of cardiovascular disease was higher in their population than in our patient sample (55.3% *vs.* 21.4% in AS patients and 60.8% *vs.* 23.1% in DISH patients, respectively), arguably explaining the higher mortality rates in their study. Schoenfeld *et al.* described the outcome of patients with AS and DISH, compared to age- and gender-matched control patients, after treatment for cervical spine fractures.[193] After three months 37.5% of AS patients, 7.4% of DISH patients and 7.0% of control patients had died; after three years the mortality was 62.5%, 29.6% and 32.6%, respectively. The mean age of their patient population was approximately eleven years higher than our study cohort, possibly explaining the increased mortality rates. Since data on in-hospital mortality were available only, total mortality may have been underreported in the present study.

Multivariable logistic regression analysis showed that the parameters age and presence of DISH were independently and statistically significantly associated with mortality in this

cohort; indicating that a patient with DISH has an increased risk of mortality after a spinal fracture, further increasing with advancing age. Patients with AS and DISH were on average five years older than control patients in our study population. Although this difference was statistically significant, it is not clear whether this finding alone can explain the large differences in clinical outcome. Many previously published reports suggested the increased mortality in elderly trauma patients to originate from the presence of (more) comorbidities.[85;144] In the present study we could not confirm this finding; the Charlson comorbidity score was not statistically different between AS, DISH or control patients and it was not associated with mortality. Other studies, however, demonstrated advancing age to be associated with increased mortality in trauma patients, regardless of co-morbidity.[1;113] The authors from these studies suggested that elderly patients often have factors impairing bodily homeostasis during stress including thin skin, less body fat and decreased cardiac output, leading to higher complication and mortality rates after trauma.[47;220] Conditions related to the metabolic syndrome and strongly associated with DISH, such as obesity, hypertension and type 2 diabetes mellitus, were relatively infrequent in this cohort compared to the literature. In the study of Mader *et al.*, for instance, obesity was present in 83% of hospitalized DISH patients, hypertension in 87% and type 2 diabetes mellitus in 49% of patients.[131] The percentages of these conditions in patients with DISH from our cohort were 50.0%, 23.1% and 30.8%, respectively. It can be argued that comorbidity may have been underreported in the present study or patients were affected by comorbidities not yet diagnosed.[41;108] The reason for high mortality in spine trauma patients with DISH is unclear, although the general patient profile (established associations with obesity, type 2 diabetes mellitus, hypertension, cardiovascular disease, advanced age) in combination with neurological deficit seems to contribute to an unfavorable clinical course.

In concurrence with previous publications, we suggest that surgical treatment may be beneficial for patients with ASD.[79] An established concept in fracture management holds that unstable fractures are painful and usually take longer to fuse, compared to stable fracture configurations.[184] Both the AO classification and the recently introduced Thoracolumbar Injury Classification and Severity Score (TLICS) include fracture morphology and integrity of the ligamentous complex to determine whether a fracture would benefit from surgical stabilization (TLICS also incorporates neurological status in this process).[133;169] Assessment by these injury classification systems of the three-column fractures frequently observed in ASD patients, would usually lead to a recommendation of operative fixation.

Some limitations of the present study can be identified. A retrospective study design may often lead to underreporting of comorbidities and mortality and introduce (inclusion) bias. We tried to minimize this potential bias by consulting several patient registries and reviewing both electronic- and hard copy medical records. The mean duration of follow up was relatively short. Patients with AS referred to our institution for treatment of their fractures were often transferred back to the initial hospital for aftercare; possibly explaining the shorter follow up duration in patients with AS (mean follow up 9.1 ± 8.1 months), compared to patients with DISH (11.8 ± 9.6 months) and controls (12.2 ± 8.8 months).

Additionally, some patients were discharged to rehabilitation centers or nursing homes while others may have deceased after discharge. In this study we confirmed DISH to be more prevalent than AS, contrasting the results from a recently published literature review on spinal fractures in ASD patients where AS outnumbered DISH; probably reflecting the low awareness for the latter disorder.[236] The prevalence of DISH may even further increase the coming decades, because of its association with lifestyle related risk factors such as obesity and type 2 diabetes mellitus. Clinicians should suspect an ankylosing spinal disorder in every adult trauma patient but particularly so in males over 50 years of age with one or more of the following conditions: hypertension; obesity and type 2 diabetes mellitus.[41;108;202] Physicians should be aware of the possible dangers and difficulties associated with spinal fractures in patients with an ASD and take appropriate measures to prevent (secondary) neurological worsening. Based on the results from this study the following conclusions could be drawn:

- Fractures in the ankylosed spine can result from low energy trauma
- Spinal fractures in ASD patients are often highly unstable and frequently represent a hyperextension configuration
- Patient delay and doctor delay often prevent timely diagnosis of fractures in patients with ASD
- Unstable fracture configurations frequently lead to neurological deficits
- Neurological deficits rarely improve irrespective of treatment
- According to general fracture principles three-column fractures benefit from surgical stabilization
- Patients with ASD and a spinal fracture have higher complication and mortality rates than control patients
- Independent risk factors for mortality after a spinal fracture are increasing age and the presence of DISH
- As the prevalence of DISH will increase in the coming decades due to its association with sedentary lifestyle related factors, physicians should be prepared to admit more trauma patients with DISH

CHAPTER 7

Future directions and clinical considerations

In this thesis we aimed to explore whether diffuse idiopathic skeletal hyperostosis (DISH) represents a true clinical entity with possible associated morbidity, instead of a radiological curiosity, as was previously suggested by some authors.[92;192] By the research performed for this thesis, we were able to demonstrate in **chapter 3** that the prevalence of DISH was relatively high in the Netherlands compared to previous reports and, since DISH is associated with ageing and metabolic disorders such as obesity and type 2 diabetes mellitus, its prevalence is likely to rise in the coming decades. It is possible that metabolic conditions associated with DISH may have been present more frequently in patients visiting the outpatient clinic of internal medicine, than in the general population; this may explain the relatively high prevalence of DISH in this particular cohort. To get a better understanding of the prevalence of DISH in a normal 'healthy' population a large cohort of normal individuals should be screened for the presence of DISH. It would be very difficult, rather impossible, to get permission of the medical ethical committee to expose such a large and asymptomatic population to radiographic examinations.

As an alternative, we have collaborated with the Rotterdam Study, which is a population based prospective cohort study of neurologic, cardiovascular, locomotor and ophthalmologic diseases in the elderly.[84] In 1990, during the first 'wave' of this study all 10,275 inhabitants of the Ommoord district, a suburb of Rotterdam, the Netherlands, aged 55 and older were invited to participate in this study. Of these 7,983 subjects (78%) agreed to do so and were included in the study. At baseline comprehensive interviews were conducted covering: general information, activities of daily living, medical history, medical consumption, medication, joint complaints, smoking, life events, family history and socioeconomic status. Anthropometrical and biochemical variables were measured at the research center. Radiological assessment of the hands, hips and vertebral column was performed. We started by reviewing the spinal radiographs of 2,000 randomly selected individuals of this cohort for the presence of DISH to investigate the prevalence of DISH in this cohort. Since many determinants are known for these individuals we will investigate risk factors contributing to the development of DISH in more detail, get an understanding of the progression of DISH over the years and explore the possible morbidity and/or impact on quality of life in individuals with DISH. This work is currently analyzed and its first results will be available soon.

Another aim of the present thesis was to investigate the morphological characteristics of the ossifications in DISH, to better understand the fracture mechanisms typical for this disorder. We learned about the spatial characteristics of DISH in **chapter 4** and hypothesized on its influence on biomechanics in case of fracture; supposedly in DISH the fractures will be localized in the vertebral body, where ossification was minimal, instead of through the intervertebral disc, where ossification was maximal. This hypothesis needs further verification, however, which can be accomplished by reviewing the fracture patterns in relation with the trauma mechanisms in the trauma population of our institution in more detail. In the first article on this cohort, which can be found in **chapter 6**, we did not look into this subject yet, since this was beyond the scope of the article. We will continue to

include more patients into the database, in order to obtain numbers large enough to refute or accept this hypothesis. Additionally, it would be interesting to investigate fracture patterns in relation to trauma mechanisms in more detail in an experimental setting. By using a standardized model to create different types of spinal fractures (e.g. compression, hyperextension and shear type fractures) in normal, ankylosing spondylitis (AS) and DISH cadaveric spines, we could investigate the magnitude of forces needed to result in specific fracture patterns and types in ankylosed and control spines.

More work is to be done on the subject of morphological characteristics of the ossifications in DISH. The findings of the study presented in **chapter 4** do not inform us about the histological characteristics, ultrastructure or yield strength of the ossified soft tissues. Histological descriptions of DISH are limited in literature; it is not known whether these ossifications (or calcifications) consist of 'mature' lamellar bone. To get more insight on this subject the histological aspects of the ossifications in DISH will be investigated. We have collected and prepared regions of interest at several spinal levels in embalmed cadaveric specimens with DISH and identical levels in unaffected control specimens. These regions of interest, *i.e.* ossified soft tissues attached to native osseous structures, are currently being processed in to histological sections, after which the analysis of the histological features of DISH by means of light microscopy will be performed.

Clinical considerations

As was shown in **chapter 2** and **6** patients with an ankylosing spinal disorder (ASD) and a spinal fracture represent a vulnerable patient category, because these fractures are highly unstable and may easily displace. Since DISH is associated with increasing age and symptoms associated with the 'metabolic syndrome' such as hypertension, obesity and type 2 diabetes mellitus, this category of trauma patients represents a major challenge for medical professionals. The presence of pre-existent spinal deformities, radiological abnormalities masking spinal fractures and low awareness for possible significant complications of DISH constitute other difficulties that can be encountered while caring for these patients. This section will give some recommendations for managing patients with ASDs to physicians who treat these patients on a daily basis; *e.g.* orthopedic (spine) surgeons, radiologists and emergency department staff.

The common practice in pre-hospital care, as advocated by the pre-hospital trauma life support (PHTLS) guidelines, is to immobilize trauma patients with a cervical collar and headblocks and strap them to a long spine board until in-hospital history taking combined with physical and radiological examinations has definitely ruled out spinal fractures.[6] This can turn out disastrous for patients with AS or DISH. Patients with ASDs have a rigid instead of a flexible spinal column and often exhibit pre-existing spinal deformities, such as a hyperkyphosis of the thoracic spine.[156] Strapping a patient with a pre-existent spinal deformity to a long spine board may be experienced as uncomfortable, yet in the presence

of a spinal fracture this practice should be regarded as dangerous. By immobilizing a patient with a spinal deformity in a position that is different from his/her normal posture, one may induce fracture dislocation which may cause or worsen neurological deficit. In order to protect the spinal column in patients with ASD and to prevent dislocation of spinal fractures, the patient should be immobilized in a position approximating the pre-trauma situation, according to pre-existent curvatures of the spine, and supported with cushions or sandbags before the patient can be strapped down to the spine board for hospital transfer. Manipulations and transfers of the patient should be kept to a minimum and should be performed using the 'logroll' maneuver by adequately skilled medical professionals to prevent fracture dislocation.
Many case-reports have presented cases of difficult endotracheal intubation in patients with DISH, because of exuberant ossifications in the cervical spine, therefore, it is important to be prepared for intubation difficulties and have additional equipment and experienced staff readily available ('get help' principle).[163] Prolonged bag-valve mask ventilation or establishing a surgical airway in case of a compromised airway should be considered as safe alternatives in a trauma setting.[10;152]

A delay in diagnosis is a frequently described problem in patients with AS or DISH, since it may be difficult to immediately diagnose fractures. Delayed diagnosis may be caused by the patient, who delays to seek medical attention after a minor incident (patient's delay). Many patients suffer from baseline back pain that may not be easily distinguished from fracture pain, by both patients and doctors. On the other hand, delay in diagnosis may occur when the fracture is not timely recognized by the physician (doctor's delay). Doctor's delay may be caused by a low level of suspicion based on the patient's history, since fractures in the ankylosed spine are frequently caused by trivial events. In case of DISH, little awareness for the condition and its potential dangers may also lead to doctor's delay. Additionally, radiographs of patients with ASD may be difficult to interpret, due to pre-existing pathologic osseous changes and/or insufficient visualization of vulnerable regions such as the cervicothoracic junction.[80]

As a general rule, we suggest that if a spinal fracture is suspected in any patient with AS or DISH, especially in cases where a neurological deficit is present, thorough radiographic examinations (by CT and/or MRI scanning if necessary) of the complete spine should be obtained without further delay. The presence of ankylosed spine segments on radiographs should render the treating physician suspicious to look for unstable spine fractures in that particular patient. In that case, a specialized orthopedic (spinal) surgeon and/or radiologist should be consulted without hesitation.

CHAPTER 8

Summary and conclusions

References

Nederlandse samenvatting

Dankwoord

Curriculum Vitae

Summary and conclusions

The predominant objective of this thesis was to investigate the extent of the clinical relevance of diffuse idiopathic skeletal hyperostosis (DISH) and its associated morbidity. During the exploration we focused on the current and expected prevalence of DISH in the Netherlands, the clinical outcome of patients with an ankylosing spinal disorder (ASD) after spinal fractures and the characteristics of the 'flowing wax' morphology of DISH with respect to fracture mechanisms specific for this condition. In this chapter the results of the studies performed for this thesis are summarized by addressing the research questions that were formulated in **chapter 1**.

What can be learned from previously published articles about the clinical outcome of patients with ankylosing spinal disorders with traumatic spinal fractures?

In **chapter 2** we reviewed the available literature on spinal fractures in patients with ASD. We pooled the articles previously published on this subject and compared the treatment, neurological function and complications of patients with ankylosing spondylitis (AS) and DISH. Although the AS and DISH study groups were comparable with respect to gender ratio and follow up duration, the mean age and the number of polytrauma patients were significantly higher in the DISH group; making direct comparison of the outcome parameters difficult. Since all papers were of retrospective design and were therefore assigned a low level of evidence, we can conclude that the evidence on this topic is extremely limited.[161] The small number of papers describing patients with DISH possibly reflects the low awareness for this disorder, since the prevalence of DISH is much higher that the prevalence of AS. Despite the methodological drawbacks of the included articles some interesting conclusions could be drawn from this review.

Patients with ASD often sustain a different type of fracture than non-ankylosed patients. In the normal 'healthy' trauma population spinal fractures usually originate from high energy trauma such as a motor vehicle accident or fall from height, whereas in patients with DISH and AS fractures were most frequently caused by low energy trauma, such as a ground level fall. The majority of fractures in patients with AS and DISH were localized in the cervical spine. The cervical region is most vulnerable for fractures, even in a 'healthy' spine, because of the smaller vertebral bodies, oblique articular facets, weaker muscle protection and the relative mobility of the heavy skull on the cervical spine.[196] It has previously been suggested by several authors that fractures tend to occur at the junction between mobile and fused spinal segments, while others reported an association between the number of contiguously ankylosed segments and increased fracture instability.[80;124;164] It seems that the biomechanically vulnerable cervicothoracic junction becomes even more susceptible to injury in case of ankylosis.

In patients with DISH the fracture was more often localized in the vertebral body, while in AS the fractures were more frequently localized in the IVD. This disorder specific fracture pattern has previously been highlighted by several authors.[73;164] It can be expected that the ankylosed spines resulting from AS and DISH have different modes of failure, since

these disorders constitute different pathological entities. In AS the IVD becomes weak as a result of functional degradation and loss of elasticity; while in DISH the IVD is bridged with exuberant ossifications, making this part the strongest in the DISH affected spine. Unfortunately, detailed fracture patterns were underreported in the included studies, especially for AS patients, making it impossible to draw solid conclusions on this subject.

Additionally, the clinical course of this fragile patient category deserves careful consideration. Delayed fracture diagnosis frequently occurred in both AS and DISH patients. In patients with AS delayed diagnosis was caused by doctor and patient related factors. Since patients with ASD often have pre-existing back pain, patients and doctors may not directly be alarmed if changes occur after a trivial trauma. In addition, radiographs of patients with ASD may be difficult to interpret due to pre-existing pathologic osseous changes, which may also lead to doctor's delay. We found that in patients with DISH, delay in diagnosis was solely caused by doctor's delay, possibly because of low awareness for this condition.

The clinical outcome of both patients with AS and DISH sustaining a spinal fracture was very poor. Many patients with AS and DISH displayed a neurological deficit at admission; yet worsening of neurological function was also reported and could result from inadequate immobilization, inconsiderate transfer or application of a supporting collar on a previously deformed cervical spine. These numbers are of major concern when compared to the results from the literature review describing (healthy and considerably younger) individuals with traumatic spine fractures by Verlaan *et al.*[228] We can hypothesize that patients with traumatic fractures of the ankylosed spine are not only susceptible to initial neurological deficit, but also to secondary neurological deterioration due to highly unstable fracture configurations between the fused segments. Treatment, whether it was operative or nonoperative, did not improve neurological function for most patients.

In patients with ASD the complication and mortality rates were high compared to previously healthy individuals with traumatic spine fractures, both after surgical and conservative treatment. Since patients with ankylosed spines were on average older and probably had more co-morbidities than the general trauma population, it is likely that these factors influenced clinical outcome. DISH is associated with obesity, type 2 diabetes and advancing age and these factors may have contributed to the even higher mortality rates in DISH patients compared to AS patients.

The prevalence of AS is stable and is estimated to be 0.05 – 1.4%. DISH is a much more common disorder, with prevalences around 15 – 25% in elderly patients, but the awareness for the disorder is still low among many clinicians. Acknowledging the association of DISH with typical traits of modern affluent societies (obesity and diabetes for example) its prevalence and degree of expression can be expected to increase during the coming decades, so clinicians should be prepared to admit more trauma patients with DISH.

Despite the previously mentioned drawbacks of this study, we concluded that the clinical outcome of patients with ASD is considerably worse compared to the general trauma population, with respect to neurological outcome, complications and mortality. Many AS and DISH patients displayed a neurological deficit, which was unlikely to improve after

operative or nonoperative treatment. The results from the systematic review resulted in the following objectives for the consecutive studies in this thesis: to explore the current prevalence of DISH in a general Dutch population; to further explore the rates in neurological deficit, complications and mortality in the population of trauma patients at our own institution and to get a better understanding of the exact morphology of the ossification in DISH, in relation to fracture characteristics.

What is the current prevalence of DISH in the Netherlands and what trends can be expected for the future?

In **chapter 3** we investigated the prevalence of DISH by screening the conventional radiographs of 501 patients visiting the outpatient clinic of internal medicine for a first consultation. We found the overall prevalence in this outpatient population of our institution to be 17.0%, which is high compared to the available literature. Previously described prevalences range from around 3% in studies regarding Finland but published 25 years ago, to 6% in a recently investigated cohort in Budapest, Hungary.[96;107] On the contrary, the prevalence in our cohort is comparable to prevalences in recent studies in Italy and the USA.[167;234] There are several possible explanations for the differences in prevalence around the world. It is likely that genetic factors contribute to the pathophysiology of DISH; this hypothesis may be illustrated by the fact that DISH also differs between different dog breeds.[112] Furthermore, it is generally accepted that the prevalence of DISH is likely to be higher in (out)patient populations, such as the population of Weinfeld in the USA and ours, since these patients are more likely to suffer from conditions that are associated with DISH, such as obesity and type 2 diabetes mellitus. It can be argued that the various studies used different criteria to diagnose DISH and investigated different age groups, making it difficult to compare the results. Finally, it can be hypothesized that the prevalences reported in the older studies and the study from Budapest are lower than more recent publications from Western Europe or the USA, because factors that are strongly related to DISH, such as obesity and type 2 diabetes mellitus, came across Eastern Europe later than the Western societies. The calories available per person per day (the amount of food bought) has continuously increased in most parts of the world from the 1970s onwards, but not in Eastern Europe.[241] It is likely that the populations that were investigated in these studies, either around 1970 in Western Europe or more recently in Eastern Europe, had not been exposed to the predominant risk factors for DISH, that are associated with increased nutritional intake resulting in obesity and subsequent metabolic disorders. The recent prevalences in Italy and the USA are comparable to ours and support this theory, since these lifestyle related conditions have been upon these countries approximately at the same time as the Netherlands.

Interestingly, we found a higher prevalence of pre-stage DISH (two level bridging ossifications) in females than in males. We hypothesize that DISH develops at a younger age and progresses faster in males; leading to a higher prevalence of DISH in males at any given age than in females. Several authors previously suggested that DISH is a more prevalent disease in males than in females. By means of logistic regression analysis we

were able to demonstrate that male gender and increasing age are significant risk factors for developing DISH. The diagnosis of DISH was not mentioned in the original radiological reports. This could be explained by the focus on specific cardiac/pulmonary/abdominal pathology when the radiologist was pursuing clinical questions. However, a low of awareness for DISH cannot be ruled out.
It was concluded that the prevalence of DISH was higher than expected in this outpatient cohort and that male gender and increasing age are significant risk factors for DISH. Since DISH is associated with metabolic disorders such as type 2 diabetes mellitus and obesity, lifestyle related conditions that seem to have become endemic in Western urbanized societies; DISH is likely to become a more frequent and therefore more important disease in the coming decades.

What can be learned about the morphology of the spinal ossifications in DISH and do characteristics of this morphology explain fracture patterns in DISH?

In the literature review it was noticed that spinal fractures in DISH seemed to occur more frequently through the vertebral body, as opposed to AS where fractures often occur at the level of the IVD. We were interested to see what could be learned about the exact morphology of DISH with respect to these disorder specific fracture characteristics. In the experiments described in **chapter 4** we quantified the mean area of the anterolateral ossifications mass (ALOM) in DISH with CT scans of human cadaveric specimens with DISH at several levels; the mid-vertebral body level, mid-IVD level and in-between adjacent caudal and cranial levels. The difference in mean ALOM was significant between these levels, meaning that the largest ALOM area was found at the level of the IVD and smallest ALOM area at the mid-vertebral body level. The finding that the mean ALOM is the largest at the mid-IVD level does not inform us about the structure or yield strength of the ossified soft tissue mass in DISH, but it can be hypothesized that the significantly larger area of ALOM at the IVD-level and adjacent caudal/cranial levels compared to the mid-vertebral body level could lead to a solid bridge between two adjacent endplates, leaving the mid-vertebral level the weakest link in the DISH affected spine.
In conclusion, the mean ALOM area was consistently found to be the largest at the mid-IVD level, compared to the mid-vertebral and adjacent cranial/caudal levels, suggesting predisposition for fractures through the vertebral body, where the new bone formation was minimal.

Is the morphology of the spinal ossifications in DISH influenced by the presence of a vascular structure?

In the second part of this study we investigated whether the presence or absence of a vascular structure influences the morphology of the ossifications in DISH. It has been previously suggested that the presence of a (pulsating) blood vessel may inhibit new bone formation, which is illustrated by the predilection place for DISH on the right side of the thoracic spine, contralateral of the descending aorta on the left side of the spine. In

concordance with this hypothesis a few case-reports have presented patients with *situs viscerum inversus* and DISH, where ossifications were located at the left side of the thoracic spine.[31;35] Forestier and Rotes-Querol already reported in their original report that the flowing ossifications in the thoracic spine were 'grooved' by the vertebral arteries.[65]
In the present study we investigated the localization of the ALOM related to the AP axis and to the vertebral segmental arteries (VSAs). It was found that the extent of ALOM area was associated with the counter-clockwise position of the ALOM centroid relative to the AP axis, meaning the larger the ossification mass, the further away from the aorta is was localized; this finding did not reach statistical significance, however. The right-sided localization of the ALOM is highly suggestive for the function of the aorta as natural barrier for new bone formation, since ossification can only take place more distant from this vascular structure.
In the clinical CTA study we showed the VSAs to be situated at the level of the mid-vertebral body in both DISH cases and controls. This finding suggests that the VSAs are fixed natural barriers for new bone formation, possibly resulting in the characteristic 'flowing candle wax' appearance of DISH. A possible drawback to this study might be that patients under monitoring for aneurysms of the abdominal aorta might not be ideal as study objects, since pre-existent vascular pathology could have influenced the location, orientation and diameter of branching VSAs. To our knowledge there have been no recordings of an association between abdominal aneurysms and aberrant VSAs, so this potential study limitation is probably not overtly important.
We conclude that the arterial system, indeed, plays a role in the morphology of soft tissue ossifications in DISH. The predilection position for the ossifications in DISH was further away from the aorta and the VSAs were consistently localized at the mid-vertebral level, where ossification was minimal, suggesting that these arteries prevented new bone formation.

Is the bone mineral density of the spine in DISH different than in controls?

The subject of increased bone formation was further explored in the study reported in **chapter 5**. The exuberant ossifications displayed on conventional radiographs of DISH patients can give the impression of skeletal robustness and, in accordance with this impression, increased bone mineral density (BMD) has sporadically been reported in patients with DISH.[43;76;186] These studies used different methods for measuring BMD, however, which makes it difficult to compare or interpret the results. Retrospectively, it is possible that BMDs were artificially increased by the presence of the ossified soft tissues characteristic for DISH in the scanning field during BMD measurements.
To quantitatively investigate the possible influence of the spinal ossifications on BMD measurements, we measured BMDs in cadaveric spines affected by DISH using different experimental orientations and compared the result to measurements in identical orientations in specimens without DISH. The results of the study showed that the presence of the ossifications in the scanning field consistently led to higher BMDs in DISH specimens, leading to a potential overestimation of BMD ranging from 23.6% to 39.0%,

depending on the scanning orientation. The BMD of the vertebral body itself was not higher in DISH specimens, as was demonstrated by BMDs in the left (unaffected) half of the anteroposterior scan in DISH cases that were not significantly different from the BMDs in controls.
The contribution of the ossifications to the BMD measurements varied within the experimental scanning orientations; the differences were most profound when the ossifications were maximally projected in the field of view and less distinctive when the ossifications were minimally present in the scanning field. These differences were also present in control specimens, but less prominent. It is unknown to what extent the presence of the posterior elements of the spine influenced the BMD measurements, but the influence was equal in DISH specimens and in controls.
We measured BMD in the thoracic spine (T4 – T11) in this study, because these regions displayed features of DISH most prominently. Secondly, the ossified ligament is most asymmetric (right sided) in the thoracic spine, which is hypothesized to be caused by the presence of the aorta on the left side of the spine; therefore it was feasible to include or exclude the ossifications during scanning. In clinical practice BMD is usually measured in the lumbar spine (L2 – L4), where ossifications also frequently occur and tend to be protruding rather than flowing.[11] The asymmetry of the ossifications observed in the thoracic spine is usually not seen in the lumbar spine, probably due to the more distant (ventral) location of the abdominal aorta from the spine. The potential overestimation of BMD in DISH patients may therefore be different in the lumbar spine, but is expected to follow the same mechanism as the thoracic spine and may therefore be considerable.
We conclude from our results that BMD of the vertebral body in DISH patients does not differ from *vertebral* BMD in controls; however, the influence of the ossifications on BMD measurements is substantial when ossifications are present in the scanning field. This may lead to an overestimation of the true vertebral BMD in DISH patients with conventional methods; for instance, normal BMD values could imply osteopenia or osteoporosis in patients with DISH. Clinicians should therefore be aware that routine AP spinal measurement of BMD may be unreliable in patients with DISH.

Is the clinical outcome after a traumatic spine fracture different for patients with ankylosing spinal disorders compared to control patients?

The results of the literature review in **chapter 2** suggested that patients with ASD are at risk for poor outcome after a spinal fracture, since rates in neurological deficits, complications and mortality were significantly higher in patients with ASD compared to the general trauma population. Since this review was based on small retrospective case-reports and case-series only, we were interested to learn whether a review of the trauma population of our own institution would confirm these results. In the study described in **chapter 6** we retrospectively investigated all patients over the age of 50 years who were admitted with a traumatic spine fracture between 2003 and 2009. In accordance with the literature review, patients with ASD were approximately five years older than control patients and predominantly of male gender. Type 2 diabetes mellitus and obesity were

more frequently reported in patients with DISH, compared to patients with AS and controls.

In patients with ASD fracture diagnosis was frequently delayed. Fractures in patients with AS and DISH often resulted from minor trauma, such as falls from a standing or sitting position; possibly leading to low awareness for fractures among treating physicians. Difficult interpretation of radiological examinations showing pathological osseous changes to the spine may also have resulted in doctor's delay. Since many patients with AS (71.4%) and DISH (42.5%) in this cohort were referrals from other hospitals, compared to controls (30.6%), a longer period of time elapsed between fracture diagnosis and definitive treatment in these patients.

Patients with ASD often display different fracture configurations, compared to trauma patients without spinal ankylosis. In the 'general' spine trauma population hyperextension fractures are rarely seen; in their study of 1445 spine fractures Magerl *et al*. observed this type of fracture in 0.2% of patients.[133] In this cohort type B *extension* fractures were observed in 64.3% of AS patients and 45.5% of DISH patients. Some authors previously hypothesized that trauma mechanisms that would not lead to fractures in a flexible spine, can result in fractures in the ankylosed spine due to AS or DISH.[40;73] Advanced ankylosis may lead to increased lever arms on which forces can act during trauma, resulting in hyperextension fractures after a simple backward fall or low-velocity rear-impact motor vehicle accident.[25] Moreover, since surrounding and stabilizing ligaments are also involved in the process of ankylosis, fractures typically propagate through all three columns and tend to result in highly unstable configurations in patients with ASD.

Many patients with AS or DISH were admitted with a neurological deficit (57.1% and 30.0%, respectively), which can be directly related to the unstable fracture configurations and the propensity of this type of fracture to displace. In the majority of patients neurological function did not improve, regardless of treatment strategy initiated. Some patients improved one ASIA grade while only one patient improved two ASIA grades, observations consistent with previous publications.[32] In 12.6% of the control patients from this cohort a neurological deficit was present; this percentage is considerably higher than normally described in literature and probably reflects a referral bias.[228]

Complication and mortality rates were significantly higher in patients with ASD compared to controls; after surgical treatment 87.5% of AS patients and 85.7% of DISH patients had at least one complication, which was 100% and 68.4% following conservative treatment, respectively. In addition, 15.0% of DISH patients, 7.1% of AS patients and 2.7% of controls died during hospitalization. Statistical analysis with multiple logistic regression showed the parameters age and presence of DISH to be independently, statistically significantly associated with mortality in this cohort; indicating that a patient with DISH has an increased risk of mortality after a spinal fracture, which further increases with advancing age. In this cohort patients with AS and DISH were on average five years older than control patients; this difference was statistically significant, however, it is not clear whether this finding alone explains the poor outcome of ASD patients. Many previously published reports suggested the increased mortality in elderly trauma patients to originate from the presence of (more) comorbidities.[85;144] In the present study we could

not confirm this finding, since the Charlson comorbidity score was not statistically different among AS, DISH or control patients and it was not associated with mortality. Other studies demonstrated that advancing age was associated with increased mortality in trauma patients, regardless of co-morbidity.[1;113] Since elderly patients have often thinner skin, less body fat and decreased cardiac output they are less able to maintain bodily homeostasis in case of stress; which leads to more complications and mortality after trauma.[47;220] Conditions related to the metabolic syndrome and strongly associated with DISH, such as obesity, hypertension and type 2 diabetes mellitus, were relatively infrequent in this cohort compared to other sources in literature.[131] Co-morbidity may have been underreported in this study cohort, but it is also possible that patients were affected by comorbidities not diagnosed (yet).[41;108] The reason for high mortality in spine trauma patients with DISH remains unclear, although the general patient profile (established associations with obesity, type 2 diabetes mellitus, hypertension, cardiovascular disease, advanced age) in combination with neurological deficit seems to contribute to an unfavorable outcome.

It was suggested that surgical treatment may be beneficial for patients with ASD over conservative treatment. Both the AOSpine classification and the recently introduced Thoracolumbar Injury Classification and Severity Score (TLICS) propagate that the morphology (*e.g.* compression, extension and shear/rotation) and stability of fractures determine whether surgical stabilization is indicated.[133;169] Assessment of the three-column fractures frequently observed in ASD patients by these injury classification systems, would typically lead to a recommendation of operative fixation.

Some limitations of this study should be considered. Retrospective study designs may lead to underreporting of comorbidities and mortality and can introduce (inclusion) bias. We tried to minimize this potential bias by consulting several patient registries and reviewing both electronic- and hard copy medical records.

In this study cohort of trauma patients we confirmed DISH to be more prevalent than AS. The prevalence of DISH will further increase in the coming decades, since DISH is associated with lifestyle related conditions such as obesity and type 2 diabetes mellitus.[41;108;202] Clinicians should suspect an ASD in every adult trauma patient, but particularly in males over 50 years of age with obesity, hypertension and type 2 diabetes mellitus. Physicians should be aware of the possible dangers and difficulties associated with spinal fractures in patients with an ASD and take appropriate measures to prevent (secondary) neurological worsening.

General conclusions

From the studies presented in this thesis the following conclusions can be drawn: first of all we demonstrated that the prevalence of DISH in the Netherlands was higher than expected and relatively high compared to other sources in literature. The prevalence of DISH in the Netherlands was found be comparable to recent published prevalences in First world countries, in which individuals have been exposed to the same risk factors for

DISH as in the Netherlands; particularly increased nutritional intake and decreased physical activity leading to obesity and associated metabolic disorders.[153;241] By means of logistic regression analysis we demonstrated that the diagnosis DISH was statistically significant related to male gender and increasing age. Based on these findings we suggest that the prevalence of DISH will increase in the coming decades, not only as a result of demographic ageing, which is becoming more and more apparent in Western societies, but more importantly because DISH seems to be highly related to obesity and diabetes mellitus type 2, disorders that have become endemic worldwide as a result of modern-day sedentary lifestyle and high-fat energy-dense diets.[202;240]

In the second part of this thesis the morphology of the ossifications of DISH was investigated in relation with the biomechanics and characteristics of fracture patterns in DISH. In cadaveric spines with DISH the ossification mass was measured with CT scanning, demonstrating that the ossification mass was maximal at the level of the IVD and minimal at the level of the vertebral body. This finding may explain the predilection for fractures through the vertebral body in DISH; since the ossifications provide a solid bridge spanning over the IVD space between two adjacent endplates, the vertebral body becomes the weakest link in the DISH affected spine.
We also demonstrated that the presence of a vascular structure indeed influences the morphology of the ossifications in DISH, as was previously suggested by a few other authors.[51;65] The larger the mean area of the ossification was, the further away from the aorta it was localized; suggesting that the new bone formation could only take place more distant from this pulsating structure. In addition, we demonstrated that the VSAs were consistently localized at the mid-vertebral level in both DISH specimens and controls, where the ossification was minimal. Although these findings do not provide insight in causality, they highly suggest that new bone formation does not take place in the proximity of vascular structures.

With respect to the new bone formation in association with increased bone mineral density (BMD) we demonstrated the BMD in DISH not to be elevated in the vertebral body. We measured BMDs in cadaveric human spines with DISH from different experimental orientations, either including or excluding the soft tissue ossifications in the DXA scanning field, and compared the results with measurements in exactly the same orientations in control specimens without DISH. We demonstrated that the ossifications projected in the field of view influenced BMD measurements, depending on the orientation in which BMD was measured. BMDs in the (unaffected) left half of the anteroposterior scan did not significantly differ from control BMDs. The findings of this study imply that BMD measurements in DISH patients may be unreliable when the ossifications are present in the field of view.

Finally we investigated whether the presence of an ASD influenced clinical outcome after a spinal fracture. In order to learn more about this subject, we performed a literature review and a retrospective review of the medical histories of patients with a spinal fracture in our

own institution. We can conclude that the outcome of patients with ASD was considerably poorer than the outcome of the general trauma population. Patients with ASD were admitted with a neurological deficit associated with their injury more frequently, leading to higher complication and mortality rates. Establishing a timely diagnosis can be more difficult in patients with AS and DISH, because fractures often result from trivial trauma and may be masked or obscured on radiographs because of extensive pathological osseous changes. Because of unstable (hyperextension) fracture configurations, operative treatment may be beneficial over nonoperative treatment in this patient category. Neurological deficit after a spinal fracture is a well known and notorious complication of longstanding AS, but DISH and its possible disastrous outcome is still underestimated by many clinicians. By performing the research for this thesis we have increased the knowledge on this subject, however, awareness among physicians must be raised still. Because of the global demographic ageing and the increase in metabolic conditions such as obesity and type 2 diabetes mellitus, which have become endemic in the past few decades, the prevalence of DISH will increase in the future. Therefore, clinicians should be prepared to care for more trauma patients with DISH.

References

1. Aitken LM, Burmeister E, Lang J *et al.* Characteristics and outcomes of injured older adults after hospital admission. J Am Geriatr Soc 2010;58:442-9.
2. Akman MN, Karatas M, Kilinc S *et al.* Double spinal cord injury in a patient with ankylosing spondylitis. Spinal Cord 1999;37:305-7.
3. Al-Herz A, Snip JP, Clark B *et al.* Exercise therapy for patients with diffuse idiopathic skeletal hyperostosis. Clin Rheumatol 2008;27:207-10.
4. Alaranta H, Luoto S, Konttinen YT. Traumatic spinal cord injury as a complication to ankylosing spondylitis. An extended report. Clin Exp Rheumatol 2002;20:66-8.
5. Amamilo SC. Fractures of the cervical spine in patients with ankylosing spondylitis. Orthop Rev 1989;18:339-44.
6. American College of Surgeons. Advanced Trauma Life Support for doctors, student course manual. Chicago, IL: American College of Surgeons 1997.
7. American Spinal Injury Association IMSoP. International standards for neurologic and functional classification of spinal cord injury. Chicago, IL: ASIA/IMSOP 1992.
8. Anderson LD, D'Alonzo RT. Fractures of the odontoid process of the axis. J Bone Joint Surg Am 1974;56:1663-74.
9. Ariza-Ariza R, Hernandez-Cruz B, Collantes E *et al.* Work disability in patients with ankylosing spondylitis. J Rheumatol 2009;36:2512-6.
10. Aziz ES, Thompson AR, Baer S. Difficult laryngeal mask insertion in a patient with Forestier's disease. Anaesthesia 1995;50:370.
11. Baim S, Leonard MB, Bianchi ML *et al.* Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Pediatric Position Development Conference. J Clin Densitom 2008;11:6-21.
12. Baron M, Tator CH, Little H. Hangman's fracture in ankylosing spondylitis preceded by vertical subluxation of the axis. Arthritis Rheum 1980;23:850-5.
13. Barsamian JG, Cobb LW, Bremer AM *et al.* Radiographic, clinical, and histopathologic evaluation with surgical treatment of Forestier's disease. Oral Surg Oral Med Oral Pathol 1985;59:136-41.
14. Belanger TA, Rowe DE. Diffuse idiopathic skeletal hyperostosis: musculoskeletal manifestations. J Am Acad Orthop Surg 2001;9:258-67.
15. Bernini PM, Floman Y, Marvel J *et al.* Multiple thoracic spine fractures complicating ankylosing hyperostosis of the spine. J Trauma 1981;21:811-4.
16. Biressi PC, Mussa L.. Radiological and anatomicopathological studies of hyperostosing discosomatic arthrosis of the dorsal spine (synonyms: candied-sugar spine; moniliform hyperostosis; senile ankylosing hyperstosis; hyperstotic spondylosis, etc.). Reumatismo. 1957;9:1-37.
17. Bjorkengren AG, Sartoris DJ, Shermis S *et al.* Patterns of paravertebral ossification in the prehistoric saber-toothed cat. Am J Roentgenol 1987;148:779-82.
18. Bloom RA. The prevalence of ankylosing hyperostosis in a Jerusalem population - with description of a method of grading the extent of the disease. Scand J Rheumatol 1984;13:181-9.
19. Bobyn JD, Mortimer ES, Glassman AH *et al.* Producing and avoiding stress shielding. Laboratory and clinical observations of noncemented total hip arthroplasty. Clin Orthop Relat Res 1992;274:79-96.
20. Boriani S, Romano B. Spinal lesions due to hyperextension in ankylosing spondylitis. Ital J Orthop Traumatol 1983;9:365-8.
21. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369:1379-90.
22. Broom MJ, Raycroft JF. Complications of fractures of the cervical spine in ankylosing spondylitis. Spine 1988;13:763-6.

23. Bundrick TJ, Cook DE, Resnik CS. Heterotopic bone formation in patients with DISH following total hip replacement. Radiology 1985;155:595-7.
24. Burke DC. Hyperextension injuries of the spine. J Bone Joint Surg Br 1971;53:3-12.
25. Burkus JK, Denis F. Hyperextension injuries of the thoracic spine in diffuse idiopathic skeletal hyperostosis. Report of four cases. J Bone Joint Surg Am 1994;76:237-43.
26. Butcher N, Balogh ZJ. The definition of polytrauma: the need for international consensus. Injury 2009;40 Suppl 4:S12-S22.
27. Byrnes MC, McDaniel MD, Moore MB *et al.* The effect of obesity on outcomes among injured patients. J Trauma 2005;58:232-7.
28. Bywaters EGL, Forestier J. Ankylosing hyperostosis. Reports and Abstracts of VI European Congress of Rheumatology (illustrated glossary of terminology) 1967;472-80.
29. Callahan EP, Aguillera H. Complications following minor trauma in a patient with diffuse idiopathic skeletal hyperostosis. Ann Emerg Med 1993;22:1067-70.
30. Canci A, Marchi D, Caramella D *et al.* Coexistence of melorheostosis and DISH in a female skeleton from Magna Graecia (Sixth Century BC). Am J Phys Anthropol 2005;126:305-10.
31. Carile L, Verdone F, Aiello A *et al.* Diffuse idiopathic skeletal hyperostosis and situs viscerum inversus. J Rheumatol 1989;16:1120-2.
32. Caron T, Bransford R, Nguyen Q *et al.* Spine fractures in patients with ankylosing spinal disorders. Spine 2010;35:E458-E464.
33. Chhem RK, Schmit P, Faure C. Did Ramesses II really have ankylosing spondylitis? A reappraisal. Can Assoc Radiol J 2004;55:211-7.
34. Chong CF. Fracture of the delicate bamboo: a diagnostic pitfall. Ann Emerg Med 2004;44:88-9.
35. Ciocci A. Diffuse idiopathic skeletal hyperostosis (DISH) and situs viscerum inversus. Report of a single case. Clin Exp Rheumatol 1987;5:159-60.
36. Clark E, Preston P, Wates A *et al.* DISHphagia - a difficult problem to swallow. Rheumatology (Oxford) 2003;42:1422-3.
37. Corke CF. Spinal fracture and paraplegia after minimal trauma in a patient with ankylosing vertebral hyperostosis. BMJ 1981;282:2035.
38. Cornefjord M, Alemany M, Olerud C. Posterior fixation of subaxial cervical spine fractures in patients with ankylosing spondylitis. Eur Spine J 2005;14:401-8.
39. Crubezy E, Trinkaus E. Shanidar 1: a case of hyperostotic disease (DISH) in the middle Paleolithic. Am J Phys Anthropol 1992;89:411-20.
40. De Peretti F, Sane JC, Dran G *et al.* Ankylosed spine fractures with spondylitis or diffuse idiopathic skeletal hyperostosis: Diagnosis and complications. Rev Chir Orthop Reparatrice Appar Mot 2004;90:456-65.
41. Denko CW, Malemud CJ. Body mass index and blood glucose: correlations with serum insulin, growth hormone, and insulin-like growth factor-1 levels in patients with diffuse idiopathic skeletal hyperostosis (DISH). Rheumatol Int 2006;26:292-7.
42. Detwiler KN, Loftus CM, Godersky JC *et al.* Management of cervical spine injuries in patients with ankylosing spondylitis. J Neurosurg 1990;72:210-5.
43. Di Franco M., Mauceri MT, Sili-Scavalli A *et al.* Study of peripheral bone mineral density in patients with diffuse idiopathic skeletal hyperostosis. Clin Rheumatol 2000;19:188-92.
44. DiGiovanna JJ. Isotretinoin effects on bone. J Am Acad Dermatol 2001;45:S176-S182.
45. DiGiovanna JJ, Helfgott RK, Gerber LH *et al.* Extraspinal tendon and ligament calcification associated with long-term therapy with etretinate. N Engl J Med 1986;315:1177-82.
46. Ebo D, Goethals L, Bracke P *et al.* Dysphagia in a patient with giant osteophytes: case presentation and review of the literature. Clin Rheumatol 2000;19:70-2.
47. Edwards M, Ley E, Mirocha J *et al.* Defining hypotension in moderate to severely injured trauma patients: raising the bar for the elderly. Am Surg 2010;76:1035-8.
48. Einsiedel T, Kleimann M, Nothofer W *et al.* Special problems and management in lesions of cervical spine affected by Bechterew's disease. Unfallchirurg 2001;104:1129-33.

49. Einsiedel T, Schmelz A, Arand M *et al.* Injuries of the cervical spine in patients with ankylosing spondylitis: experience at two trauma centers. J Neurosurg Spine 2006;5:33-45.
50. El Masry MA, Badawy WS, Chan D. Combined anterior and posterior stabilisation for treating an unstable cervical spine fracture in a patient with long standing ankylosing spondylitis. Injury 2004;35:1064-7.
51. El Miedany YM, Wassif G, El Baddini M. Diffuse idiopathic skeletal hyperostosis (DISH): is it of vascular aetiology? Clin Exp Rheumatol 2000;18:193-200.
52. Eviatar E, Harell M. Diffuse idiopathic skeletal hyperostosis with dysphagia (a review). J Laryngol Otol 1987;101:627-32.
53. Exner G, Botel U, Kluger P *et al.* Treatment of fracture and complication of cervical spine with ankylosing spondylitis. Spinal Cord 1998;36:377-9.
54. Fast A, Parikh S, Marin EL. Spine fractures in ankylosing spondylitis. Arch Phys Med Rehabil 1986;67:595-7.
55. Fazl M, Bilbao JM, Hudson AR. Laceration of the aorta complicating spinal fracture in ankylosing spondylitis. Neurosurgery 1981;8:732-4.
56. Feldtkeller E, Lemmel EM, Russell AS. Ankylosing spondylitis in the pharaohs of ancient Egypt. Rheumatol Int 2003;23:1-5.
57. Feldtkeller E, Vosse D, Geusens P *et al.* Prevalence and annual incidence of vertebral fractures in patients with ankylosing spondylitis. Rheumatol Int 2006;26:234-9.
58. Ferree BA, Wieser M, Clarke RP. Hyperextension spinal fracture. Orthop Rev 1989;18:1061-4.
59. Finkelstein JA, Chapman JR, Mirza S. Occult vertebral fractures in ankylosing spondylitis. Spinal Cord 1999;37:444-7.
60. Fishman EK, Magid D. Cervical fracture in ankylosing spondylitis: value of multidimensional imaging. Clin Imaging 1992;16:31-3.
61. Foo D, Bignami A, Rossier AB. Two spinal cord lesions in a patient with ankylosing spondylitis and cervical spine injury. Neurology 1983;33:245-9.
62. Foo D, Rossier AB. Post-traumatic spinal epidural hematoma. Neurosurgery 1982;11:25-32.
63. Foo D, Sarkarati M, Marcelino V. Cervical spinal cord injury complicating ankylosing spondylitis. Paraplegia 1985;23:358-63.
64. Forestier J, Lagier R. Ankylosing hyperostosis of the spine. Clin Orthop Relat Res 1971;74:65-83.
65. Forestier J, Rotes-Querol J. Senile vertebral ankylosing hyperostosis. Rev Rhum Mal Osteoartic 1950;17:525-34.
66. Gartman Jr. JJ, Bullitt E, Baker ML. Axis fracture in ankylosing spondylitis: case report. Neurosurgery 1991;29:590-4.
67. Garza-Mercado R. Traumatic extradural hematoma of the cervical spine. Neurosurgery 1989;24:410-4.
68. Gelineck J, De Carvalho A. Fractures of the spine in ankylosing spondylitis. RoFo 1990;152:307-10.
69. Gertzbein SD. Scoliosis Research Society. Multicenter spine fracture study. Spine 1992;17:528-40.
70. Giuffra V, Giusiani S, Fornaciari A *et al.* Diffuse idiopathic skeletal hyperostosis in the Medici, Grand Dukes of Florence (XVI century). Eur Spine J 2010;19 Suppl 2:S103-S107.
71. Gokce A, Beyzadeoglu T, Hanci L *et al.* Diffuse idiopathic skeletal hyperostosis as a cause of acute respiratory distress in early postoperative period of total knee arthroplasty. Arch Orthop Trauma Surg 2007;127:553-5.
72. Govender S, Charles RW. Fracture of the dens in ankylosing spondylitis. Injury 1987;18:213-4.
73. Graham B, Van Peteghem PK. Fractures of the spine in ankylosing spondylitis. Diagnosis, treatment and complications. Spine 1989;14:803-7.
74. Gretschel S, Estevez-Schwarz L, Hunerbein M *et al.* Gastric cancer surgery in elderly patients. World J Surg 2006;30:1468-74.
75. Grisolia A, Bell RL, Peltier LF. Fractures and dislocations of the spine complicating ankylosing spondylitis: a report of six cases. Clin Orthop Relat Res 2004;422:129-34.

76. Haara MM, Arokoski JP, Kroger H *et al.* Relative bone mineral density measured by metacarpal index (MCI) and chronic spinal syndromes: an epidemiological study. Scand J Rheumatol 2007;36:466-9.
77. Hanson JA, Mirza S. Predisposition for spinal fracture in ankylosing spondylitis. Am J Roentgenol 2000;174:150.
78. Harrop JS, Sharan A, Anderson G *et al.* Failure of standard imaging to detect a cervical fracture in a patient with ankylosing spondylitis. Spine 2005;30:E417-E419.
79. Hedlund R, Verlaan JJ. Thoracolumbar hyperextension injuries in the stiff spine. In: Vaccaro AR, Fehlings MG, Dvorak MF, eds. In: Spine and spinal cord trauma. New York: Thieme Medical Publishers Inc., 2011:391-9.
80. Hendrix RW, Melany M, Miller F *et al.* Fracture of the spine in patients with ankylosis due to diffuse skeletal hyperostosis: clinical and imaging findings. Am J Roentgenol 1994;162:899-904.
81. Hertlein H, Schams S, Lob G. Extension-distraction injury of the lumbar spine in spondylarthrosis ankylopoetica. Unfallchirurgie 1991;17:259-63.
82. Heyde CE, Robinson Y, Kayser R *et al.* Fatal complex fracture of the cervical spine in a patient with ankylosing spondylitis after a fall from a racing bicycle. Sportverletz Sportschaden 2007;21:148-51.
83. Hitchon PW, From AM, Brenton MD *et al.* Fractures of the thoracolumbar spine complicating ankylosing spondylitis. J Neurosurg 2002;97:218-22.
84. Hofman A, Grobbee DE, de Jong PT *et al.* Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol. 1991;7:403-22.
85. Hollis S, Lecky F, Yates DW *et al.* The effect of pre-existing medical conditions and age on mortality after injury. J Trauma 2006;61:1255-60.
86. Horn EM, Theodore N, Feiz-Erfan I *et al.* Complications of halo fixation in the elderly. J Neurosurg Spine 2006;5:46-9.
87. Hornick TR. Surgical innovations: impact on the quality of life of the older patient. Clin Geriatr Med 2006;22:499-513.
88. Houk RW, Hendrix RW, Lee C *et al.* Cervical fracture and paraplegia complicating diffuse idiopathic skeletal hyperostosis. Arthritis Rheum 1984;27:472-5.
89. Hughes TA, Wiles CM, Lawrie BW *et al.* Case report: dysphagia and sleep apnoea associated with cervical osteophytes due to diffuse idiopathic skeletal hyperostosis (DISH). J Neurol Neurosurg Psychiatry 1994;57:384.
90. Hunter T, Dubo HIC. Spinal fractures complicating ankylosing spondylitis. A long-term followup study. Arthritis Rheum 1983;26:751-9.
91. Hunter T, Forster B, Dvorak M. Ankylosed spines are prone to fracture. Can Fam Physician 1995;41:1213-6.
92. Hutton C. DISH ... a state not a disease? Br J Rheumatol 1989;28:277-8.
93. Iplikcioglu AC, Bayar MA, Kokes F *et al.* Magnetic resonance imaging in cervical trauma associated with ankylosing spondylitis: report of two cases. J Trauma 1994;36:412-3.
94. Irwin ZN, Arthur M, Mullins RJ *et al.* Variations in injury patterns, treatment, and outcome for spinal fracture and paralysis in adult versus geriatric patients. Spine 2004;29:796-802.
95. Israel Z, Mosheiff R, Gross E *et al.* Hyperextension fracture-dislocation of the thoracic spine with paraplegia in a patient with diffuse idiopathic skeletal hyperostosis. J Spinal Disord 1994;7:455-7.
96. Julkunen H, Heinonen OP, Knekt P *et al.* The epidemiology of hyperostosis of the spine together with its symptoms and related mortality in a general population. Scand J Rheumatol 1975;4:23-7.
97. Julkunen H, Heinonen OP, Pyorala K. Hyperostosis of the spine in an adult population. Its relation to hyperglycaemia and obesity. Ann Rheum Dis 1971;30:605-12.
98. Julkunen H, Knekt P, Aromaa A. Spondylosis deformans and diffuse idiopathic skeletal hyperostosis (DISH) in Finland. Scand J Rheumatol 1981;10:193-203.

99. Juric G, Coumas JM, Giansiracusa DF *et al.* Hemothorax - An unusual presentation of spinal fracture in ankylosing spondylitis. J Rheumatol 1990;17:263-6.
100. Kao LS, Todd SR, Moore FA. The impact of diabetes on outcome in traumatically injured patients: an analysis of the National Trauma Data Bank. Am J Surg 2006;192:710-4.
101. Kaplan SL, Tun CG, Sarkarati M. Odontoid fracture complicating ankylosing spondylitis: A case report and review of the literature. Spine 1990;15:607-10.
102. Karpman RR, Weinstein PR, Gall EP *et al.* Lumbar spinal stenosis in a patient with diffuse idiopathic skeletal hypertrophy syndrome. Spine 1982;7:598-603.
103. Kauppi M, Belt EA, Soini I. 'Bamboo spine' starts to bend - Something is wrong. Clin Exp Rheumatol 2000;18:513-4.
104. Kawabori M, Hida K, Akino M *et al.* Cervical myelopathy by C1 posterior tubercle impingement in a patient with DISH. Spine 2009;34:E709-E711.
105. Kessler T, Quintel M, Winkler H *et al.* Lethal transverse fracture through the body of C6 with tracheal lesion in ankylosing spondylitis: Case report. Unfallchirurg 1996;99:525-9.
106. Kim SK, Choi BR, Kim CG *et al.* The prevalence of diffuse idiopathic skeletal hyperostosis in Korea. J Rheumatol 2004;31:2032-5.
107. Kiss C, O'Neill TW, Mituszova M *et al.* The prevalence of diffuse idiopathic skeletal hyperostosis in a population-based study in Hungary. Scand J Rheumatol 2002;31:226-9.
108. Kiss C, Szilagyi M, Paksy A *et al.* Risk factors for diffuse idiopathic skeletal hyperostosis: a case-control study. Rheumatology (Oxford) 2002;41:27-30.
109. Kiwerski J, Wieclawek H, Garwacka I. Fractures of the cervical spine in ankylosing spondylitis. Int Orthop 1985;8:243-6.
110. Knaggs RL. Spondylitis deformans. Br J Surg 1925;12:524-46.
111. Knop C, Blauth M, Buhren V *et al.* Surgical treatment of injuries of the thoracolumbar transition - part 3: Follow-up examination. Results of a prospective multi-center study by the 'Spinal' Study Group of the German Society of Trauma Surgery. Unfallchirurg 2001;104:583-600.
112. Kranenburg HC, Westerveld LA, Verlaan JJ *et al.* The dog as an animal model for DISH? Eur Spine J 2010;19:1325-9.
113. Labib N, Nouh T, Winocour S *et al.* Severely Injured Geriatric Population: Morbidity, Mortality, and Risk Factors. J Trauma 2011.
114. Lagier R, Baud CA. Diffuse enthesopathic hyperostosis - anatomical and radiological study on a macerated skeleton. RoFo 1978;129:588-97.
115. Lahoti OP, Callanan I, Reidy DP *et al.* Hidden flexion injury of the cervical spine in ankylosing spondylitis. Injury 1995;26:67-9.
116. Lange U, Pape HC, Bastian L *et al.* Operative management of cervical spine injuries in patients with Bechterew's disease. Unfallchirurg 2005;108:63-8.
117. Le Hir PX, Sautet A, Le GL *et al.* Hyperextension vertebral body fractures in diffuse idiopathic skeletal hyperostosis: a cause of intravertebral fluidlike collections on MR imaging. Am J Roentgenol 1999;173:1679-83.
118. Leroux JL, Legeron P, Moulinier L *et al.* Stenosis of the lumbar spinal canal in vertebral ankylosing hyperostosis. Spine 1992;17:1213-8.
119. Levine AM, Edwards CC. Fractures of the atlas. J Bone Joint Surg Am 1991;73:680-91.
120. Levine AM, Edwards CC. The management of traumatic spondylolisthesis of the axis. J Bone Joint Surg Am 1985;67:217-26.
121. Liang CL, Lu K, Lee TC *et al.* Dissociation of atlantoaxial junction in ankylosing spondylitis: case report. J Trauma 2002;53:1173-5.
122. Lifshutz J, Lidar Z, Maiman D. Thoracic aortic pseudoaneurysm after spine trauma in ankylosing spondylitis. Case report. J Neurosurg Spine 2005;2:218-21.
123. Maat GJR, Mastwijk RW, van der Velde EA. Skeletal distribution of degenerative changes in vertebral osteophytosis, vertebral osteoarthritis and DISH. Int J Osteoarchaeol 1995;5:289-98.

124. Mac Millan M., Stauffer ES. Traumatic instability in the previously fused cervical spine. J Spinal Disord 1991;4:449-54.
125. Mader R. Diffuse idiopathic skeletal hyperostosis: isolated involvement of cervical spine in a young patient. J Rheumatol 2004;31:620-1.
126. Mader R. Diffuse idiopathic skeletal hyperostosis: a distinct clinical entity. Isr Med Assoc J 2003;5:506-8.
127. Mader R. Clinical manifestations of diffuse idiopathic skeletal hyperostosis of the cervical spine. Semin Arthritis Rheum 2002;32:130-5.
128. Mader R. Diffuse idiopathic skeletal hyperostosis: time for a change. J Rheumatol 2008;35:377-9.
129. Mader R, Dubenski N, Lavi I. Morbidity and mortality of hospitalized patients with diffuse idiopathic skeletal hyperostosis. Rheumatol Int 2005;26:132-6.
130. Mader R, Lavi I. Diabetes mellitus and hypertension as risk factors for early diffuse idiopathic skeletal hyperostosis (DISH). Osteoarthritis Cartilage 2008.
131. Mader R, Novofestovski I, Adawi M *et al.* Metabolic syndrome and cardiovascular risk in patients with diffuse idiopathic skeletal hyperostosis. Semin Arthritis Rheum 2008.
132. Mader R, Sarzi-Puttini P, Atzeni F *et al.* Extraspinal manifestations of diffuse idiopathic skeletal hyperostosis. Rheumatology (Oxford) 2009;48:1478-81.
133. Magerl F, Aebi M, Gertzbein SD *et al.* A comprehensive classification of thoracic and lumbar injuries. Eur Spine J 1994;3:184-201.
134. Majercik S, Tashjian RZ, Biffl WL *et al.* Halo vest immobilization in the elderly: a death sentence? J Trauma 2005;59:350-6.
135. Malik SA, Murphy M, Connolly P *et al.* Evaluation of morbidity, mortality and outcome following cervical spine injuries in elderly patients. Eur Spine J 2008.
136. Markel DC, Graziano GP. Fracture of the S1 vertebral body in a patient with ankylosing spondylitis. J Spinal Disord 1992;5:222-6.
137. Maskery NSS, Burrows N. Cervical spine control; Bending the rules. Emerg Med J 2002;19:592-3.
138. Mata S, Fortin PR, Fitzcharles MA *et al.* A controlled study of diffuse idiopathic skeletal hyperostosis. Clinical features and functional. Medicine (Baltimore) 1997;76:104-17.
139. Mata S, Hill RO, Joseph L *et al.* Chest radiographs as a screening test for diffuse idiopathic skeletal hyperostosis. J Rheumatol 1993;20:1905-10.
140. Matan AJ, Hsu J, Fredrickson BA. Management of respiratory compromise caused by cervical osteophytes: a case report and review of the literature. Spine J 2002;2:456-9.
141. Matejka J. Hyperextension injuries of the thoracolumbar spine. Zentralbl Chir 2006;131:75-9.
142. May PJ, Raunest J, Herdmann J *et al.* Management of vertebral fractures in ankylosing spondylitis. Unfallchirurg 2002;105:165-9.
143. McCall I, El Masri W, Jaffray D. Hangman's fracture in ankylosing spondylitis. Injury 1985;16:483-4.
144. McGwin G, Jr., Maclennan PA, Fife JB *et al.* Preexisting conditions and mortality in older trauma patients. J Trauma 2004;56:1291-6.
145. McKenzie MK, Bartal E, Pay NT. A hyperextension injury of the thoracic spine in association with diffuse idiopathic skeletal hyperostosis. Orthopedics 1991;14:895-8.
146. Mears T. Acupuncture for back pain in a patient with Forestier's disease (diffuse idiopathic skeletal hyperostosis/DISH). Acupunct Med 2002;20:102-4.
147. Miller FH, Rogers LF. Fractures of the dens complicating ankylosing spondylitis with atlantooccipital fusion. J Rheumatol 1991;18:771-4.
148. Mody GM, Charles RW, Ranchod HA *et al.* Cervical spine fracture in diffuse idiopathic skeletal hyperostosis. J Rheumatol 1988;15:129-31.
149. Moreau APM, Willcox N, Brown MF. Immobilisation of spinal fractures in patients with ankylosing spondylitis: Two case reports. Injury 2003;34:372-3.
150. Morgan JP, Stavenborn M. Disseminated idiopathic skeletal hyperostosis (DISH) in a dog. Vet Radiol Ultrasound 1991;32:65-70.

151. Murray GC, Persellin RH. Cervical fracture complicating ankylosing spondylitis. A report of eight cases and review of the literature. Am J Med 1981;70:1033-41.
152. Naik B, Lobato EB, Sulek CA. Dysphagia, obstructive sleep apnea, and difficult fiberoptic intubation secondary to diffuse idiopathic skeletal hyperostosis. Anesthesiology 2004;100:1311-2.
153. Nestle M, Jacobson MF. Halting the obesity epidemic: a public health policy approach. Public Health Rep. 2000;115:12-24.
154. Neville AL, Brown CV, Weng J *et al.* Obesity is an independent risk factor of mortality in severely injured blunt trauma patients. Arch Surg 2004;139:983-7.
155. Olerud C, Frost A, Bring J. Spinal fractures in patients with ankylosing spondylitis. Eur Spine J 1996;5:51-5.
156.Olivieri I, D'Angelo S, Cutro MS *et al.* Diffuse idiopathic skeletal hyperostosis may give the typical postural abnormalities of advanced ankylosing spondylitis. Rheumatology (Oxford) 2007;46:1709-11.
157. Ono K, Yonenobu K, Miyamoto S *et al.* Pathology of ossification of the posterior longitudinal ligament and ligamentum flavum. Clin Orthop Relat Res 1999;18-26.
158. Oppenheimer A. Calcification and ossification of vertebral ligaments (spondylitis ossificans ligamentosa): roentgen study of pathogenesis and clinical significance. Radiology 1942;38:160-73.
159. Oppenlander ME, Orringer DA, La MF *et al.* Dysphagia due to anterior cervical hyperosteophytosis. Surg Neurol 2009;72:266-70.
160. Ott VR. Uber die spondylosis hyperostotica. Schweiz Med Wochenschr 1953;83:790-9.
161. Oxford Centre for Evidence-based Medicine. Levels of Evidence. [http://www.cebm.net/index.aspx?o=1025]. 2001.
162. Ozgocmen S, Ardicoglu O. Odontoid fracture complicating ankylosing spondylitis. Spinal Cord 2000;38:117-9.
163. Ozkalkanli MY, Katircioglu K, Ozkalkanli DT *et al.* Airway management of a patient with Forestier's disease. J Anesth. 2006;20:304-6.
164. Paley D, Schwartz M, Cooper P *et al.* Fractures of the spine in diffuse idiopathic skeletal hyperostosis. Clin Orthop Relat Res 1991;267:22-32.
165. Papadopoulos MC, Chakraborty A, Waldron G *et al.* Lesson of the week: exacerbating cervical spine injury by applying a hard collar. BMJ 1999;319:171-2.
166. Papakostas K, Thakar A, Nandapalan V *et al.* An unusual case of stridor due to osteophytes of the cervical spine: Forestier's disease. J Laryngol Otol 1999;113:65-7.
167. Pappone N, Lubrano E, Esposito-del PA *et al.* Prevalence of diffuse idiopathic skeletal hyperostosis in a female Italian population. Clin Exp Rheumatol 2005;23:123-4.
168. Pascal-Moussellard H, Drossard G, Cursolles JC *et al.* Myelopathy by lesions of the craniocervical junction in a patient with forestier disease. Spine 2006;31:E557-E560.
169. Patel AA, Dailey A, Brodke DS *et al.* Thoracolumbar spine trauma classification: the Thoracolumbar Injury Classification and Severity Score system and case examples. J Neurosurg Spine 2009;10:201-6.
170. Payer M. Surgical management of cervical fractures in ankylosing spondylitis using a combined posterior-anterior approach. J Clin Neurosci 2006;13:73-7.
171. Peh WCG. A 33-year-old man presented with progressive neck pain and a subjective sensation of neck instability. Diagnosis: type II dens fracture complicating ankylosing spondylitis. Australas Radiol 2001;45:101-3.
172. Peh WCG, Ho EKW. Fracture of the odontoid peg in ankylosing spondylitis: case report. J Trauma 1995;38:361-3.
173. Podolsky SM, Hoffman JR, Pietrafesa CA. Neurologic complications following immobilization of cervical spine fracture in a patient with ankylosing spondylitis. Ann Emerg Med 1983;12:578-80.

174. Pofahl WE, Pories WJ. Current status and future directions of geriatric general surgery. J Am Geriatr Soc 2003;51:S351-S354.
175. Ravn-Pedersen P, Jurik AG. Diffuse idiopathic skeletal hyperostosis in a patient with right-sided aorta. Rontgenblatter 1988;41:495-6.
176. Ravussin E, Valencia ME, Esparza J *et al.* Effects of a traditional lifestyle on obesity in Pima Indians 8. Diabetes Care 1994;17:1067-74.
177. Resnick D, Niwayama G. Diffuse idiopathic skeletal hyperostosis (DISH): ankylosing hyperostosis of Forestier and Rotes-Querol. In: Diagnosis of Bone and Joint disorders. 3rd ed. Philadelphia: WB Saunders, 1995:1563-604.
178. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology 1976;119:559-68.
179. Resnick D, Shaul SR, Robins JM. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier's disease with extraspinal manifestations. Radiology 1975;115:513-24.
180. Rogers J, Waldron T. DISH and the monastic way of life. Int J Osteoarchaeol 2001;11:357-65.
181. Rogers J, Waldron T, Dieppe P *et al.* Arthropathies in paleopathology: the basis of classification according to most probable cause. J Archaeol Sci 1987;14:179-93.
182. Roosen K, Wissing H, Grote W *et al.* Operative stabilization of fractures in the cervical spine in Bechterew's disease. Unfallchirurg 1985;88:215-8.
183. Rothschild BM. Diffuse idiopathic skeletal hyperostosis as reflected in the paleontologic record: dinosaurs and early mammals. Semin Arthritis Rheum 1987;17:119-25.
184. Rüedi TP, Buckley RE, Moran CG. AO Principles of Fracture Management, part 1: Principles. 2nd ed. New York: Thieme Medical Publishers, 2007.
185. Ruf M, Rehm S, Poeckler-Schoeniger C *et al.* Iatrogenic fractures in ankylosing spondylitis - a report of two cases. Eur Spine J 2006;15:100-4.
186. Sahin G, Polat G, Bagis S *et al.* Study of axial bone mineral density in postmenopausal women with diffuse idiopathic skeletal hyperostosis related to type 2 diabetes mellitus. J Womens Health (Larchmt) 2002;11:801-4.
187. Samartzis D, Anderson DG, Shen FH. Multiple and simultaneous spine fractures in ankylosing spondylitis: case report. Spine 2005;30:E711-E715.
188. Sarzi-Puttini P, Atzeni F. New developments in our understanding of DISH (diffuse idiopathic skeletal hyperostosis). Curr Opin Rheumatol 2004;16:287-92.
189. Savolaine ER, Ebraheim NA, Stitgen S *et al.* Aortic rupture complicating a fracture of an ankylosed thoracic spine: a case report. Clin Orthop Relat Res 1991;272:136-40.
190. Scapinelli R. Compression of the inferior vena cava due to diffuse idiopathic skeletal hyperostosis. Rev Rhum Engl Ed 1997;64:198-201.
191. Schaberg Jr. FJ. Aortic injury occurring after minor trauma in ankylosing spondylitis. J Vasc Surg 1986;4:410-1.
192. Schlapbach P, Beyeler C, Gerber NJ *et al.* Diffuse idiopathic skeletal hyperostosis (DISH) of the spine: a cause of back pain? A controlled study. Br J Rheumatol 1989;28:299-303.
193. Schoenfeld AJ, Harris MB, McGuire KJ *et al.* Mortality in elderly patients with hyperostotic disease of the cervical spine after fracture: an age- and sex-matched study. Spine J 2011;11:257-64.
194. Schroder J, Liljenqvist U, Greiner C *et al.* Complications of halo treatment for cervical spine injuries in patients with ankylosing spondylitis - report of three cases. Arch Orthop Trauma Surg 2003;123:112-4.
195. Schwartz JB, Rackson M. Diffuse idiopathic skeletal hyperostosis causes artificially elevated lumbar bone mineral density measured by dual X-ray absorptiometry. J Clin Densitom 2001;4:385-8.
196. Secin FP, Poggi EJ, Luzuriaga F *et al.* Disabling injuries of the cervical spine in Argentine rugby over the last 20 years. Br J Sports Med 1999;33:33-6.

197. Sharma RR, Mahapatra A, Pawar SJ *et al.* Spinal cord and cauda equina compression in DISH. Neurol India 2001;49:148-52.
198. Shen FH, Samartzis D. Cervical spine fracture in the ankylosing spondylitis patient. J Am Coll Surg 2005;200:632-3.
199. Shen FH, Samartzis D. Successful nonoperative treatment of a three-column thoracic fracture in a patient with ankylosing spondylitis: existence and clinical significance of the fourth column of the spine. Spine 2007;32:E423-E427.
200. Shimizu S, Tanaka R, Kan S *et al.* Origins of the segmental arteries in the aorta: an anatomic study for selective catheterization with spinal arteriography. Am J Neuroradiol 2005;26:922-8.
201. Smith CF, Pugh DG, Polley HF. Physiologic vertebral ligamentous calcification: an aging process. Am J Roentgenol Radium Ther Nucl Med 1955;74:1049-58.
202. Smyth S, Heron A. Diabetes and obesity: the twin epidemics. Nat Med 2006;12:75-80.
203. Spagnola AM, Bennett PH, Terasaki PI. Vertebral ankylosing hyperostosis (Forestier's disease) and HLA antigens in Pima Indians. Arthritis Rheum 1978;21:467-72.
204. Sreedharan S, Li YH. Diffuse idiopathic skeletal hyperostosis with cervical spinal cord injury - a report of 3 cases and a literature review. Ann Acad Med Singapore 2005;34:257-61.
205. Stechison MT, Tator CH. Cervical myelopathy in diffuse idiopathic skeletal hyperostosis. Case report. J Neurosurg 1990;73:279-82.
206. Straiton N. Fractures of the lower vertebral column in ankylosing spondylitis. Br J Clin Pract 1987;41:933-4.
207. Strohm PC, Zwingmann J, Bley TA *et al.* Injuries of the cervical spine with Forestier's disease: problems in the diagnostic and surgical management. Unfallchirurg 2006;109:905-9.
208. Sundararajan V, Henderson T, Perry C *et al.* New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57:1288-94.
209. Surin VV. Fractures of the cervical spine in patients with ankylosing spondylitis. Acta Orthop Scand 1980;51:79-84.
210. Sutro CJ, Ehrlich DE, Witten M. Generalized juxta-articular ossification of ligaments of the vertebral column and of the ligamentous and tendinous tissues of the extremities; (also known as Bechterew's disease, osteophytosis and spondylosis deformans). Bull Hosp Joint Dis 1956;17:343-57.
211. Taggard DA, Traynelis VC. Management of cervical spinal fractures in ankylosing spondylitis with posterior fixation. Spine 2000;25:2035-9.
212. Tait TJ, Barlow G, Iveson JMI. Cervical spine fracture in ankylosing spondylitis: a case of 'auto-fracture'. Br J Rheumatol 1998;37:467-8.
213. Taljanovic MS, Hunter TB, Wisneski RJ *et al.* Imaging characteristics of diffuse idiopathic skeletal hyperostosis with an emphasis on acute spinal fractures: review. Am J Roentgenol 2009;193:S10-9, Quiz.
214. Tashjian RZ, Majercik S, Biffl WL *et al.* Halo-vest immobilization increases early morbidity and mortality in elderly odontoid fractures. J Trauma 2006;60:199-203.
215. Tetzlaff JE, Yoon HJ, Bell G. Massive bleeding during spine surgery in a patient with ankylosing spondylitis. Can J Anaesth 1998;45:903-6.
216. Thorngren KG, Liedberg E, Aspelin P. Fractures of the thoracic and lumbar spine in ankylosing spondylitis. Arch Orthop Trauma Surg 1981;98:101-7.
217. Thumbikat P, Hariharan RP, Ravichandran G *et al.* Spinal cord injury in patients with ankylosing spondylitis: a 10-year review. Spine 2007;32:2989-95.
218. Tico N, Ramon S, Garcia-Ortun F *et al.* Traumatic spinal cord injury complicating ankylosing spondylitis. Spinal Cord 1998;36:349-52.
219. Tiesenhausen K, Thalhammer M, Koch G *et al.* Traumatic aortic rupture in ankylosing spondylitis - a lethal complication. Unfallchirurg 2001;104:1101-3.
220. Tornetta III P, Mostafavi H, Riina J *et al.* Morbidity and mortality in elderly trauma patients. J Trauma 1999;46:702-6.

221. Trent G, Armstrong GWD, O'Neil J. Thoracolumbar fractures in ankylosing spondylitis: high-risk injuries. Clin Orthop Relat Res 1988;227:61-6.
222. Ullrich H. Goethe's skull and skeleton. Anthropol Anz 2002;60:341-68.
223. Upadhyay SS, Ho EK, Hsu LC. Positioning for plain spinal radiography producing paraplegia in a patient with ankylosing spondylitis. Br J Radiol 1991;64:549-51.
224. Urrutia J, Bono CM. Long-term results of surgical treatment of dysphagia secondary to cervical diffuse idiopathic skeletal hyperostosis. Spine J 2009;9:e13-e17.
225. Utsinger PD. Diffuse idiopathic skeletal hyperostosis. Clin Rheum Dis 1985;11:325-51.
226. Van der Linden S. Ankylosing spondylitis. Kelley WN,Harris S, Ruddy S *et al.*: Textbook of Rheumatology, ed 5.Philadelphia: WB Saunders 1997;2:969-82.
227. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
228. Verlaan JJ, Diekerhof CH, Buskens E *et al.* Surgical treatment of traumatic fractures of the thoracic and lumbar spine: a systematic review of the literature on techniques, complications, and outcome. Spine 2004;29:803-14.
229. Verlaan JJ, Öner FC, Maat GJ. Diffuse idiopathic skeletal hyperostosis in ancient clergymen. Eur Spine J 2007.
230. Vesovic-Potic V, Mustur D, Stanisavljevic D *et al.* Relationship between spinal mobility measures and quality of life in patients with ankylosing spondylitis. Rheumatol Int 2009;29:879-84.
231. Villari N, Fornaciari G, Lippi D *et al.* Scenes from the past: the Medici Project: radiographic survey. Radiographics 2009;29:2101-14.
232. Vives MJ, Harris C, Reiter MF *et al.* Use of stand-up magnetic resonance imaging for evaluation of a cervicothoracic injury in a patient with ankylosing spondylitis. Spine J 2008;8:678-82.
233. Wade W, Saltzstein R, Maiman D. Spinal fractures complicating ankylosing spondylitis. Arch Phys Med Rehabil 1989;70:398-401.
234. 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 Radiol 1997;26:222-5.
235. Westerveld LA, van Ufford HM, Verlaan JJ *et al.* The prevalence of diffuse idiopathic skeletal hyperostosis in an outpatient population in the Netherlands. J Rheumatol 2008;35:1635-8.
236. Westerveld LA, Verlaan JJ, Öner FC. Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. Eur Spine J 2009;18:145-56.
237. Whang PG, Goldberg G, Lawrence JP *et al.* The Management of Spinal Fractures in Patients with Ankylosing Spondylitis or Diffuse Idiopathic Skeletal Hyperostosis: A Comparison of Treatment Methods and Clinical Outcomes. J Spinal Disord Tech 2009;22:77-85.
238. Winkelstein BA, Myers BS. The biomechanics of cervical spine injury and implications for injury prevention. Med Sci Sports Exerc 1997;29:S246-S255.
239. Woodard JC, Poulos PW, Jr., Parker RB *et al.* Canine diffuse idiopathic skeletal hyperostosis. Vet Pathol 1985;22:317-26.
240. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. Tech Rep Ser 894 2000;1-253.
241. World Resources Institute. Earth Trends: Nutrition: Calorie supply per capita. [http://earthtrends.wri.org/searchable_db/index.php?theme=8&variable_ID=212&action=select_countries]. May 2011.
242. Wrobel CJ, Meyer W. Diffuse idiopathic skeletal hyperostosis. J Neurosurg 2000;93:341-2.
243. Wu CT, Lee ST. Spinal epidural hematoma and ankylosing spondylitis: case report and review of the literature. J Trauma 1998;44:558-61.
244. Young JS, Cheshire JE, Pierce JA *et al.* Cervical ankylosis with acute spinal cord injury. Paraplegia 1977;15:133-46.

Nederlandse samenvatting

Het doel van dit proefschrift was om te onderzoeken of diffuse idiopathic skeletal hyperostosis (DISH) een klinisch relevantie aandoening is en of patiënten met DISH hinder van deze aandoening ondervinden. Door DISH ontstaan op allerlei plekken in het lichaam ossificaties (verbeningen) op plaatsen waar ligamenten en pezen aanhechten aan bot. Hierdoor kunnen pijnklachten en verminderde beweeglijkheid ontstaan in feitelijk alle gewrichten. Om de diagnose DISH te stellen moet er sprake zijn van ossificatie over tenminste vier aaneensluitende wervels, waarbij het beeld op de röntgenfoto lijkt op druipend kaarsvet (figuur 1).[178] Deze rechtszijdig gelokaliseerde ossificaties kunnen uiteindelijk leiden tot complete ankylose (verstijving) van de wervelkolom. De aandoening komt vaker voor bij mannen dan bij vrouwen en wordt geassocieerd met aandoeningen die te maken hebben met het metabole syndroom, zoals obesitas (overgewicht) en diabetes mellitus type 2 (ouderdomssuikerziekte).
Tijdens deze zoektocht lag de focus op de prevalentie van DISH is Nederland (hoe vaak de aandoening voorkomt) en wat de verwachtingen voor de toekomst zijn. Daarnaast hebben we onderzocht wat de klinische uitkomst was van patiënten met DISH na het doormaken van een wervelfractuur (gebroken rug), met andere woorden hoe het deze patiënten verging na een dergelijk letsel. Tenslotte onderzochten we de typische morfologie (verschijningsvorm) van DISH, die vaak wordt vergeleken met druipend kaarsvet, in relatie

Figuur 1
Typisch beeld van DISH met ossificatie over meer dan vier aaneengesloten wervels, lijkend op druipend kaarsvet.

tot de fractuurmechanismen die worden gezien bij deze aandoening. In dit hoofdstuk worden de resultaten van de studies besproken aan de hand van de vragen die gesteld zijn in **hoofdstuk 1**.

Wat kunnen we leren uit eerder gepubliceerde artikelen over de klinische uitkomst van patiënten met een ankylotische wervelkolom aandoening en een traumatische wervelfractuur?

In **hoofdstuk 2** werd een literatuuroverzicht van de beschikbare artikelen over wervelfracturen bij patiënten met een ankylotische wervelkolom aandoening gepresenteerd. Artikelen die eerder over dit onderwerp gepubliceerd zijn werden zeer kritisch gelezen, waarna de behandeling, neurologische uitkomst en complicaties bij patiënten met DISH en de ziekte van Bechterew (AS) werden vergeleken. Hoewel de groepen van patiënten met DISH en AS vergelijkbaar waren qua man/vrouw verhouding en duur van follow-up, waren de gemiddelde leeftijd en het aantal ernstig gewonde patiënten in de DISH groep significant hoger. Hierdoor werd directe vergelijking van de twee groepen vrijwel onmogelijk. Aangezien alle artikelen retrospectief waren en hierdoor niet van goede kwaliteit waren (lage level of evidence), concludeerden wij dat er zeer weinig bewijs is over dit onderwerp.[161] Het kleine aantal artikelen dat de uitkomst van patiënten met DISH beschreef geeft waarschijnlijk weer hoe weinig kennis er nog maar is over deze aandoening, aangezien de prevalentie van DISH veel hoger is dan die van AS. Ondanks de methodologische minpunten van de geïncludeerde artikelen, is het de moeite waard enkele conclusies de revue te laten passeren.
Bij patiënten met een ankylotische (verstijfde) wervelkolom aandoening is er vaak sprake van een ander type wervelfractuur dan bij patiënten zonder ankylosis van de wervelkolom. In de normale 'gezonde' populatie worden wervelfracturen vaak veroorzaakt door hoogenergetische traumata, zoals een auto-ongeluk of een val van grote hoogte. Bij patiënten met DISH en AS is een wervelfractuur echter vaak het gevolg van een laagenergetisch voorval, zoals een val uit staande of zittende positie. De meerderheid van de fracturen was gelokaliseerd in de cervicale wervelkolom (halswervelkolom). De cervicale regio is kwetsbaar voor fracturen, ook bij 'gezonde' individuen, omdat hier de wervellichamen kleiner zijn, de gewrichten schuiner verlopen en er minder bescherming door omliggende spieren is; wat resulteert in de relatieve mobiliteit van het zware hoofd ten opzichte van de wervelkolom.[196] Sommige auteurs hebben eerder gesuggereerd dat fracturen gemakkelijk optreden in de overgang van een 'normaal' en een ankylotisch gedeelte van de wervelkolom, terwijl anderen een relatie beschreven tussen het aantal gefuseerde wervellichamen en toegenomen instabiliteit van de fractuur.[80;124;164] Kennelijk is de cervicale regio, die biomechanisch al kwetsbaar is voor fracturen, nog gevoeliger voor letsel als er ankylosis bestaat in die regio.
Bij patiënten met DISH was de fractuur vaker gelokaliseerd in het wervellichaam, terwijl bij patiënten met AS de fractuur vaker in de tussenwervelschijf verliep, een fenomeen dat vaker beschreven is.[73;164] Hoewel DISH en AS beiden in het eindstadium tot complete ankylosis kunnen leiden zijn het echt verschillende pathologische entiteiten en het is dan

ook te verwachten dat ze op verschillende manieren onder krachten zullen bezwijken. In het geval van AS verzwakt de tussenwervelschijf als gevolg van functionele degradatie en verlies van elasticiteit door calcificatie (verkalking) van de tussenwervelschijf, terwijl bij DISH de extra botvormingen de tussenwervelschijf juist overbruggen, waardoor dit gedeelte het sterkste deel van de wervelkolom wordt. Helaas werden de fractuurpatronen in veel gevallen niet gedetailleerd genoeg beschreven, met name bij patiënten met AS, waardoor het niet mogelijk is hierover duidelijke conclusies te trekken.
Het klinisch beloop van deze kwetsbare patiëntencategorie verdient speciale aandacht. Zowel in patiënten met AS als met DISH werd soms de diagnose in eerste instantie gemist. Bij AS patiënten werd dit zowel door de behandelend arts als door de patiënt zelf veroorzaakt. Omdat patiënten met AS vaak chronisch rugpijn hebben is het soms lastig om fractuurpijn na een kleine val hiervan te onderscheiden, zowel voor arts als patiënt. Ook kan het dusdanig lastig zijn om de fractuur op röntgenfoto's te onderscheiden, door allerlei reeds bestaande pathologische veranderingen, dat de fractuur in eerste instantie gemist wordt. In deze review kwam het bij patiënten met DISH vaak voor dat de fractuur gemist werd de arts, waarschijnlijk omdat de aandoening nog weinig bekendheid geniet.
De klinische uitkomst van patiënten met AS en DISH na een wervelfractuur was slecht. Bij veel patiënten met AS en DISH was er neurologische uitval bij opname, maar verslechtering van het neurologisch beeld kwam ook voor; bijvoorbeeld door inadequate immobilisatie, onvoorzichtig transport naar/in het ziekenhuis of het aanbrengen van een harde halskraag bij een patiënt met een pre-existente deformiteit van de nek. Deze getallen roepen veel zorg op als ze vergeleken worden met resultaten van (gezonde en veel jongere) patiënten met traumatische wervelfracturen die door Verlaan *et al.* beschreven werden.[228] Niet alleen lijken patiënten met een ankylotische wervelkolom dus kwetsbaarder voor neurologische uitval als direct gevolg van de fractuur, maar ook voor secundaire neurologische achteruitgang doordat de fracturen een zeer instabiele configuratie hebben. In de meeste gevallen trad er geen verbetering van het neurologisch beeld op na behandeling, ongeacht of deze operatief of niet-operatief was.
Er traden veel complicaties op bij patiënten met AS en DISH en ook de mortaliteit (sterfte) was zeer hoog in vergelijking met de 'normale' populatie traumapatiënten. De patiënten in deze studie waren gemiddeld ouder en hadden waarschijnlijk meer comorbiditeit (een patiënt heeft meerdere aandoeningen tegelijkertijd), wat een verklaring kan zijn voor de slechtere uitkomst. Patiënten met DISH zijn vaak ouder en hebben vaker obesitas en diabetes mellitus type 2. Deze factoren hebben mogelijk bijgedragen aan het feit dat de mortaliteit onder DISH patiënten nog hoger was dan onder patiënten met AS.
De prevalentie van AS is stabiel en ligt tussen de 0.05 - 1.4%. DISH komt veel vaker voor, ongeveer tussen de 15 - 25% bij oudere patiënten, maar de bekendheid van deze aandoening is veel kleiner. Er vanuit gaande dat DISH te maken heeft met aandoeningen die voortkomen uit de moderne verstedelijkte maatschappij (zoals obesitas en diabetes mellitus type 2 bijvoorbeeld), is het te verwachten dat deze aandoening vaker zal voorkomen en wellicht ook ernstiger zal worden in de toekomst. Artsen moeten er dus op voorbereid worden om meer traumapatiënten met DISH te behandelen.

Ondanks de beperkingen van de artikelen die in deze studie werden geïncludeerd, kunnen we concluderen dat de klinische uitkomst van patiënten met een ankylotische wervelkolom slechter was dan van 'normale' traumapatiënten, gekeken naar neurologische uitval, complicaties en sterfte. Veel patiënten met AS en DISH hadden reeds neurologische uitval toen zij werden opgenomen in het ziekenhuis en behandeling (operatief of niet-operatief) bracht hierin meestal weinig tot geen verbetering. Op basis van de resultaten van deze studie werden de doelen voor de hierop volgende studies geformuleerd: de huidige prevalentie van DISH in Nederland te onderzoeken, de klinische uitkomst van patiënten met DISH en AS in ons eigen ziekenhuis te onderzoeken en de exacte morfologie van de nieuwe botvorming die wordt gezien bij DISH beter te begrijpen om de fractuurmechanismen te kunnen verklaren.

Wat is de prevalentie van DISH en wat kunnen we verwachten in de toekomst?

In **hoofdstuk 3** hebben we onderzocht hoe vaak de aandoening DISH voorkomt in Nederland, door de thoraxfoto's van 501 patiënten die de polikliniek van de interne geneeskunde bezochten voor een eerste consult te screenen. We vonden dat de prevalentie 17% was, wat vrij hoog is in vergelijking met de beschikbare literatuur. In eerder verschenen artikelen over dit onderwerp varieerde de prevalentie van ongeveer 3% in studies in Finland 25 jaar geleden, tot 6% in een meer recent verschenen onderzoek in Boedapest (Hongarije).[96;107] Maar er zijn recentelijk ook artikelen verschenen waarin prevalenties gevonden werden vergelijkbaar met die van ons, zoals in Italië en de Verenigde Staten.[167;234] Er zijn verschillende verklaringen voor het feit dat het voorkomen van DISH wereldwijd verschilt. Het is mogelijk dat er genetische factoren bijdragen aan de ontstaanswijze van DISH, een hypothese die mogelijk wordt ondersteund door de bevinding dat de prevalentie van DISH ook verschilt tussen diverse hondenrassen.[112] Daarnaast is het mogelijk dat de prevalentie van DISH hoger is in ziekenhuis populaties zoals die van Weinfeld in de Verenigde Staten en die van ons; zelfs in een populatie van mensen die een polikliniek bezoeken. Waarschijnlijk hebben deze individuen vaker last van aandoeningen die gerelateerd zijn aan DISH, zoals obesitas en diabetes mellitus type 2. Maar het zou ook kunnen liggen aan het feit dat verschillende studies andere criteria hanteerden om de diagnose DISH te stellen en verschillende leeftijdsgroepen onderzochten, waardoor het zeer lastig wordt de resultaten te vergelijken. Tot slot is het aannemelijk dat de prevalenties die worden gerapporteerd in oudere studies en in Boedapest lager zijn dan de cijfers uit de Verenigde Staten en West-Europa, omdat factoren die bijdragen aan het ontstaan van DISH, zoals obesitas en diabetes mellitus type 2, later in Oost-Europa zijn opgetreden dan in westerse maatschappijen. Het aantal calorieën dat per persoon beschikbaar is (de hoeveelheid voedsel die per persoon gekocht wordt) is vanaf 1970 voortdurend gestegen in de meeste gebieden in de wereld, behalve in Oost-Europa.[241] Hierdoor is het aannemelijk dat de onderzochte populaties, hetzij rond 1970 in West-Europa of meer recentelijk in Oost-Europa, (nog) niet blootgesteld waren aan de risicofactoren die waarschijnlijk het meest bijdragen aan het ontstaan van DISH, die allemaal te maken hebben met een toegenomen voedsel inname leidend tot obesitas en daarmee geassocieerde metabole

aandoeningen. De recent beschreven prevalentie van DISH in Italië en de Verenigde Staten zijn vergelijkbaar met de resultaten van ons onderzoek, hetgeen deze theorie ondersteunt, aangezien deze 'lifestyle' gerelateerde aandoeningen deze landen in dezelfde periode als Nederland hebben aangedaan.
In deze studie vonden we een hogere prevalentie van het voorstadium van DISH (verbening over drie wervels) bij vrouwen dan bij mannen. Hierdoor ontstaat de indruk dat DISH bij mannen eerder ontstaat en sneller progressief is, waardoor de prevalentie van DISH bij mannen op elke leeftijd hoger is dan bij vrouwen. Meerdere auteurs hebben eerder gesuggereerd dat DISH vaker voorkomt bij mannen dan bij vrouwen, maar in deze studie hebben wij met behulp van logistische regressie (een statistische methode) aangetoond dat het mannelijk geslacht inderdaad een risicofactor is voor het ontstaan van DISH, net als toenemende leeftijd.
De diagnose DISH werd nooit genoemd in het verslag van de beoordelend radioloog. Dit zou kunnen komen doordat de focus op specifieke cardiale/pulmonale/abdominale pathologie lag wanneer de radioloog de vraagstelling van de röntgenfoto probeerde te beantwoorden. Het kan echter ook zo zijn dat weinig radiologen (nog) bekend zijn met het fenomeen DISH en de tekenen die zichtbaar kunnen zijn op een röntgenfoto.
We concludeerden dat de prevalentie van DISH in het cohort patiënten dat onderzocht werd relatief hoog was en dat het mannelijk geslacht en toenemende leeftijd risicofactoren zijn voor het ontwikkelen van DISH. Omdat DISH is geassocieerd met metabole aandoeningen zoals obesitas en diabetes mellitus type 2, die in de toekomst alleen nog maar vaker zullen voorkomen door de toenemende vergrijzing, zal DISH een vaker voorkomende en belangrijkere aandoening worden in de komende jaren.

Wat kunnen we leren over de morfologie van de spinale ossificaties die gezien worden bij DISH en zeggen de karakteristieken van deze morfologie iets over fractuur patronen bij DISH?

In de resultaten van het literatuuroverzicht viel op dat wervelfracturen bij patiënten met DISH zich vaker bevonden in het wervellichaam, in tegenstelling tot patiënten met AS, bij wie fracturen vaker door de tussenwervelschijf lopen. Hierdoor leek het ons interessant om dieper in te gaan op de morfologie van de ossificaties van DISH in relatie tot de fractuur kenmerken specifiek voor deze aandoening. In de experimenten beschreven in **hoofdstuk 4** hebben we de gemiddelde oppervlakte van de ossificatie (genoemd anterolaterale ossificatie massa, afgekort ALOM) op verschillende niveaus gekwantificeerd door middel van CT scans van menselijke kadaver preparaten; in het midden van het wervellichaam, in het middel van de tussenwervelschijf en er precies tussenin. Het verschil in de gemiddelde oppervlakte was significant tussen deze niveaus, oftewel de grootste gemiddelde oppervlakte van de ossificatie bevond zich terplekke van de tussenwervelschijf en de kleinste gemiddelde oppervlakte bevond zich in het midden van het wervellichaam. Dit zegt ons niets over de structuur of trekkracht van deze verbeende massa, maar we kunnen wel veronderstellen dat de significant grotere oppervlakte van de ALOM op het niveau van de tussenwervelschijf leidt tot een sterke brug tussen de twee aanliggende

wervellichamen, waardoor het midden van wervel de zwakste schakel wordt in de door DISH aangedane wervelkolom.
Concluderend was de gemiddelde oppervlakte van de ossificaties consequent het grootst op het niveau van de tussenwervelschijf, vergeleken met het midden van het wervellichaam en de niveaus er tussenin. Het is aannemelijk dat hierdoor fracturen in een DISH wervelkolom gemakkelijker door het wervellichaam zullen verlopen, aangezien de nieuwe botvorming daar minimaal was.

Wordt de morfologie van de spinale ossificaties in DISH beïnvloed door een vasculaire structuur?

In het tweede deel van deze studie hebben we onderzocht of de aan- of afwezigheid van een vasculaire structuur (bloedvat) de morfologie van de ossificaties van DISH beïnvloedt. Eerder werd al door een enkele auteur gesuggereerd dat de aanwezigheid van een (pulserend) bloedvat de nieuwe botvorming kan tegengaan, bijvoorbeeld in de thoracale wervelkolom, waar de ossificaties van DISH aan de rechterkant zitten, terwijl de *aorta descendens* (dalende grote lichaamsslagader) aan de linkerkant van de wervelkolom verloopt. Deze hypothese wordt ondersteund door de bevinding dat bij patiënten met *situs viscerum inversus* (bij wie organen in spiegelbeeld zijn aangelegd) en DISH de ossificaties aan de linkerkant van de thoracale wervelkolom zaten.[31;35] Ook Forestier en Rotes-Querol noemden al in hun eerste beschrijving van de aandoening dat de vloeiende ossificaties in de thoracale wervelkolom werden 'geplooid' door dwars verlopende bloedvaten.[65]
In deze studie werd de lokalisatie van de ossificaties (wederom afgekort als ALOM) in verhouding tot de voorachterwaartse as van het wervellichaam en tot de vertebrale segmentale arteriën (VSAs) bestudeerd. We vonden dat de grootte van de ALOM was geassocieerd met positie van het geometrisch zwaartepunt ten opzichte van de voorachterwaartse as van het wervellichaam. Met andere woorden: hoe groter de oppervlakte van de ossificatie was, des te verder weg van de aorta deze gelokaliseerd was. Deze bevinding bereikte echter geen statistische significantie. Het feit dat de ossificatie aan de rechterkant van de aorta gelokaliseerd is suggereert wel dat de aorta als 'natuurlijke barrière' tegen bot nieuwvorming functioneert, aangezien de nieuwvorming alleen verder weg van de aorta lijkt plaats te vinden.
In het tweede deel van de studie werden op CTA scans van DISH patiënten en controle patiënten de lokalisaties van de VSAs bekeken; deze bleken zich bij beide groepen in het midden van het wervellichaam te bevinden. Deze bevinding suggereert dat de VSAs gefixeerde natuurlijke barrières zijn voor de nieuwe botvorming, hetgeen mogelijk resulteert in het typische uiterlijk van de ossificaties van DISH dat vaak vergeleken wordt met druipend kaarsvet. Een minpunt van de studie is mogelijk dat de patiënten die in deze studie werden geïncludeerd onder controle waren voor een aneurysma (verwijding) van de abdominale aorta (grote buikslagader), wat zou kunnen betekenen dat vooraf aanwezige aandoeningen van de bloedvaten mogelijk zouden kunnen bijdragen aan afwijkende lokalisatie, oriëntatie en diameter van de vertakkende VSAs. Voor zover ons bekend is zijn

er echter geen beschrijvingen van een mogelijke relatie tussen abdominale aneurysma's en aberrant (afwijkend) verlopende VSAs.
Er werd geconcludeerd dat het arteriële systeem inderdaad een rol speelt bij de morfologie van de ossificaties van weke delen in het kader van DISH. We vonden dat de voorkeurspositie van de ossificaties van DISH verder weg van de aorta was en dat de VSAs consequent in het midden van het wervellichaam waren gelokaliseerd, waar de ossificatie minimaal was. Hierdoor ontstaat de suggestie dat deze bloedvaten nieuwe botvorming voorkomen.

Is de botdichtheid van de wervelkolom bij DISH anders dan bij controles?

Op het onderwerp van toegenomen bot aanmaak werd verder ingegaan in **hoofdstuk 5**. De uitgebreide ossificaties die soms op röntgenfoto's van patiënten met DISH kunnen waargenomen worden geven de indruk van enorme robuustheid en sterkte van het skelet van de betreffende patiënt. Geheel in overeenstemming met deze impressie zijn er eerder artikelen verschenen waarin de botdichtheid van patiënten met DISH verhoogd was.[43;76;186] Deze studies gebruikten verschillende methodes om de botdichtheid te bepalen, wat het lastig maakt de resultaten met elkaar te vergelijken. In retrospectie is het mogelijk dat de botdichtheid kunstmatig verhoogd werd doordat de ossificaties van de weke delen, die zo karakteristiek zijn voor DISH, in het scanveld aanwezig waren tijdens de metingen.
Om kwantitatief te kunnen vaststellen wat de invloed is van de aanwezigheid van de ossificaties van de wervelkolom tijdens het verrichten van botdichtheidmetingen, hebben we de botdichtheid met behulp van DXA scanning gemeten in kadaver wervelkolommen met DISH vanuit verschillende experimentele richtingen en de resultaten vergeleken met die van preparaten zonder DISH. De resultaten van deze studie lieten zien dat de aanwezigheid van de ossificaties in het scanveld voortdurend leidde tot een significant hogere botdichtheid in DISH preparaten, waardoor een mogelijke overschatting van de botdichtheid van 23.6% tot 39.0% werd bereikt, afhankelijk van de hoek waarin gemeten werd. De botdichtheid van het wervellichaam zelf was niet hoger, zoals werd gedemonstreerd door de metingen van de botdichtheid in de (niet-aangedane) linkerhelft van de voorachterwaartse scan van DISH preparaten, die niet significant hoger waren dan die van controle preparaten.
Hoeveel de botdichtheid werd verhoogd door de aanwezigheid van de ossificaties in het scanveld, hing af van de oriëntatie waarin gescand werd: het verschil was het grootst wanneer de ossificaties maximaal aanwezig waren in het scanveld en kleiner wanneer een klein deel van de ossificaties in beeld was. Deze verschillen waren ook aanwezig in de controle preparaten, maar deze waren veel kleiner. Het is onbekend in welke mate de aanwezigheid van de posterieure elementen van de wervelkolom de botdichtheid metingen hebben beïnvloed, maar wat zeker is dat deze invloed het zelfde is geweest bij DISH en controle preparaten.
In deze studie hebben we de botdichtheid gemeten in de thoracale (borst-) wervelkolom (T4 – T11), omdat in deze regio de kenmerken van DISH het meest prominent aanwezig waren bij deze preparaten. Daarnaast zijn de ossificaties het meest asymmetrisch

(rechtszijdig) aanwezig in de thoracale wervelkolom, wat mogelijk komt door de aanwezigheid van de pulserende aorta aan de linkerkant van de wervelkolom, waardoor het in deze regio mogelijk is de ossificaties binnen of buiten het scanveld te houden. In het ziekenhuis wordt de botdichtheid meestal gemeten in de lumbale wervelkolom (L2 – L4), waar ossificaties bij DISH patiënten ook vaak voorkomen, maar vaker puntiger en grilliger van vorm zijn.[11] De asymmetrie van de ossificaties die in de thoracale wervelkolom wordt gezien, bestaat niet in die mate in de lumbale wervelkolom, waarschijnlijk omdat de aorta zich hier meer naar voren (in de richting van de buikwand) bevindt, verder weg van de wervelkolom. De mogelijke overschatting van de botdichtheid in DISH patiënten kan daardoor in de lumbale wervelkolom anders zijn, maar de verwachting is dat deze het zelfde mechanisme kent als in de thoracale wervelkolom en daardoor dus aanzienlijk zal zijn.
We concluderen uit de resultaten van deze studie dat de botdichtheid van het wervellichaam bij DISH preparaten niet anders is dan die bij controle preparaten, maar dat de invloed van de ossificaties aanzienlijk is op de botdichtheid meting zodra de ossificaties zich in het scanveld bevinden. Hierdoor kan een overschatting ontstaan van de ware botdichtheid met de conventionele meetapparatuur, waardoor een bevonden normale botdichtheid eigenlijk osteoporose (botontkalking) of osteopenie (voorstadium van botontkalking) kan betekenen bij DISH patiënten. Artsen dienen zich dus bewust te zijn van het feit dat routine voorachterwaartse metingen van de botdichtheid in de wervelkolom onbetrouwbaar kunnen zijn bij DISH patiënten.

In de klinische uitkomst na een traumatische wervelfractuur anders bij patiënten met een ankylotische wervelkolom aandoening vergeleken met controle patiënten?

De resultaten van het literatuuroverzicht in **hoofdstuk 2** suggereerden dat patiënten met een ankylotische wervelkolom aandoening veel kans hebben op een slechte uitkomst na een wervelfractuur, aangezien het aantal patiënten met neurologische uitval, complicaties en dat uiteindelijk overleed veel hoger was dan in de normale trauma populatie. Omdat dit overzicht gebaseerd was op retrospectieve onderzoeken van zeer kleine patiënten groepen, wilden we weten of deze resultaten bevestigd zouden worden door kritisch naar de trauma populatie van ons eigen ziekenhuis te kijken. In de studie beschreven in **hoofdstuk 6** hebben we retrospectief alle patiënten boven de leeftijd van 50 jaar die met een traumatische wervelfractuur tussen 2003 en 2009 werden opgenomen onderzocht. In overeenstemming met eerdere resultaten bleken de patiënten met een ankylotische wervelkolom aandoening gemiddeld vijf jaar ouder dan de controle patiënten en bestond deze groep met name uit mannen. Obesitas en diabetes mellitus type 2 kwamen vaker voor bij patiënten met DISH dan bij patiënten met AS of controle patiënten.
Bij patiënten met een ankylotische wervelkolom aandoening werd de diagnose vaak verlaat gesteld ('gemist'). De fracturen werden vaak veroorzaakt door een klein trauma, zoals een val uit staande of zittende positie, waardoor de behandelend arts wellicht niet direct dacht aan een fractuur. Daarnaast kan het moeilijk zijn de fractuur te ontdekken op een röntgenfoto, omdat hierop uitgebreide veranderingen te zien zijn als gevolg van DISH of

AS. Veel patiënten met AS (71.4%) en DISH (42.5%) van dit cohort werden verwezen vanuit een ander ziekenhuis, tegenover 30.6% van de controle patiënten, waardoor de tijdspanne tussen de fractuur diagnose en de inzet van behandeling bij deze patiënten langer was.
Patiënten met ankylotische wervelkolom aandoening hadden vaak andere fractuurtypen dan traumapatiënten zonder ankylotische wervelkolom. In de 'normale' trauma populatie worden hyperextensie (overstrekking) fracturen zelden gezien; in een enorme studie van 1445 wervelfracturen beschreven Magerl *et al.* dit type fractuur bij 0.2% van de patiënten.[133] In dit cohort werden type B extensie fracturen gezien bij 64.3% van de patiënten met AS en bij 45.5% van de patiënten met DISH. Sommige auteurs beweerden eerder al dat trauma mechanismen die bij 'gezonde' patiënten met een flexibele wervelkolom niet tot een fractuur zouden leiden, bij patiënten een akylotische wervelkolom door AS of DISH wel een fractuur tot gevolg kunnen hebben.[40;73] Vergevorderde ankylose leidt tot toegenomen hefbomen waarop krachten gemakkelijk kunnen werken tijdens een ongeval, waardoor hyperextensie fracturen gemakkelijk kunnen optreden na een simpele val achterover op de rug of een kop-staartbotsing bij lage snelheid.[25] Doordat de eromheen liggende en stabiliserende ligamenten ook meedoen aan het proces van verbening bij AS en DISH, zetten de fracturen vaak door in alle drie de kolommen van de wervelkolom, waardoor deze zeer instabiel worden.
Veel patiënten met AS en DISH hadden bij opname neurologische uitval (57.1% en 30.0%, respectievelijk), wat direct gerelateerd kan worden aan de instabiele fractuurtypen en de neiging van deze fracturen om te disloceren. In de meerderheid van de gevallen verbeterde de neurologische functie niet, ongeacht wat voor behandeling werd gegeven. Sommige patiënten verbeterden een ASIA graad, terwijl een patiënt twee ASIA gradaties verbeterde. Deze resultaten zijn in overeenstemming met eerder gepubliceerde resultaten.[32] In 12.6% van de controle patiënten was neurologische uitval aanwezig; omdat dit percentage veel hoger is dan in de literatuur beschreven wordt, is dit waarschijnlijk direct het gevolg van een referral bias (alleen zeer ernstig gewonde patiënten of patiënten met zeer moeilijk behandelbare letsels worden naar een academisch (tertiair) ziekenhuis verwezen).[228]
Complicaties en sterfte kwamen significant vaker voor bij patiënten met een ankylotische wervelkolom aandoening; na operatieve behandeling had 87.5% van de patiënten met AS en 85.7% van de patiënten met DISH op zijn minst een complicatie, hetgeen 100% en 68.4% was na niet-operatieve behandeling, respectievelijk. Tijdens de opname in het ziekenhuis stierf 15.0% van de DISH patiënten, 7.1% van de AS patiënten en 2.7% van de controle patiënten. Statistische analyse door middel van multipele logistische regressie analyse liet zien dat de parameters leeftijd en DISH onafhankelijk, statistisch significant geassocieerd waren met mortaliteit. Dit betekent dat een patiënt met DISH meer kans heeft om te overlijden na het doormaken van een wervelfractuur; een kans die nog verder toeneemt naarmate de patiënt ouder wordt. In dit cohort waren de patiënten met AS en DISH gemiddeld vijf jaar ouder dan de controle patiënten; een verschil dat significant was, maar het is onduidelijk of dit verschil de slechtere uitkomst van patiënten met een ankylotische wervelkolom aandoening verklaart. Er is veel geschreven over de slechte uitkomst van oudere patiënten die een trauma doormaken en veel auteurs schrijven de

hogere kans op sterfte toe aan de aanwezigheid van (meer) comorbiditeit.[85;144] Deze aanname konden we in de huidige studie niet bewijzen, aangezien de Charlson Comorbidity Index niet verschilde tussen AS, DISH en controle patiënten en ook niet geassocieerd was met sterfte. Andere studies bewezen dat toegenomen leeftijd geassocieerd was met sterfte, ongeacht de aan- of afwezigheid van comorbiditeit.[1;113] Omdat oudere patiënten vaak een dunnere huid, minder lichaamsvet en een verminderde pompfunctie van het hart hebben, zijn zij minder goed in staat om homeostase in het lichaam te bewaren ten tijde van stress, hetgeen kan leiden tot complicaties en zelfs sterfte na een trauma.[47;220]

In dit cohort zagen we relatief minder vaak aandoeningen die gerelateerd zijn aan het metabole syndroom en ook sterk geassocieerd zijn met DISH, zoals obesitas, diabetes mellitus type 2 en hypertensie (hoge bloeddruk), dan dat op grond van de literatuur te verwachten is.[131] Het kan zijn dat comorbiditeiten ondergerapporteerd werden, maak het kan ook zo zijn dat patiënten dergelijke aandoeningen al wel hadden, maar dat de diagnose (nog) niet gesteld was.[41;108] De werkelijke reden waarom patiënten met DISH een dergelijke hoge kans hebben op sterfte na een wervelfractuur blijft onduidelijk, maar het algemene profiel van een patiënt met DISH (obesitas, diabetes mellitus type 2, hypertensie, hart-en vaatziekten, oudere leeftijd) in combinatie met neurologische uitval lijken bij te dragen aan een ongunstige uitkomst.

We suggereerden dat operatieve behandeling beter zou zijn voor patiënten met een ankylotische wervelkolom aandoening dan niet-operatieve behandeling. Zowel de AOSpine classificatie als de recent geïntroduceerde Thoracolumbar Injury Classification and Severity Score (TLICS) geven aan dat de morfologie (compressie, extensie en rotatie) en de stabiliteit van de fractuur uitmaken of operatieve stabilisatie geïndiceerd is.[133;169] Als de instabiele fracturen die gezien worden bij patiënten met AS en DISH met deze classificaties zouden worden beoordeeld, zou op grond hiervan operatieve behandeling geadviseerd worden.

Enkele minpunten van de huidige studie moeten in acht genomen worden. Retrospectieve studies kunnen leiden tot onderrapportage van comorbiditeiten en sterfte en kunnen bias (onzuiverheid in het onderzoek) introduceren. We hebben geprobeerd deze potentiële bias te minimaliseren door meerdere patiënten registraties te gebruiken en zowel de elektronische als papieren patiënten statussen te analyseren.

In dit cohort van traumapatiënten hebben we bevestigd dat DISH vaker voorkomt dan AS. De prevalentie van DISH zal nog verder toe nemen in de toekomst, omdat DISH geassocieerd is met lifestyle gerelateerde aandoeningen zoals obesitas en diabetes mellitus type 2.[41;108;202] Clinici zouden een ankylotische wervelkolom aandoening moeten overwegen in elke trauma patiënt, maar met name als de betreffende patiënt van het mannelijk geslacht is, ouder dan 50 jaar en last heeft van obesitas, hypertensie en/of diabetes mellitus type 2. Artsen zouden bekend moeten zijn met de mogelijke gevaren en complicaties die geassocieerd zijn met wervelfracturen bij patiënten met een ankylotische wervelkolom aandoening, zodat ze tijdig maatregelen kunnen treffen om (secundaire) neurologische verslechtering te voorkomen.

Algemene conclusies

Uit de studies die in het kader van dit proefschrift werden verricht kan het volgende worden geconcludeerd: ten eerste demonstreerden we dat de prevalentie van DISH in Nederland hoger dan verwacht was en relatief hoog in vergelijking met eerder gepubliceerde studies. De prevalentie van DISH in Nederland was vergelijkbaar met gevonden prevalenties in andere landen in de Eerste wereld, waarin de bevolking is blootgesteld aan dezelfde risicofactoren voor het ontwikkelen van DISH als in Nederland; vooral toegenomen voedselinname en verminderde lichamelijk activiteit leidend tot overgewicht en aanverwante metabole stoornissen.[153;241] Door middel van logistische regressie analyse vonden we dat de diagnose DISH statistisch significant gerelateerd was aan het mannelijk geslacht en toegenomen leeftijd. Gebaseerd op deze bevindingen verwachten we dat de prevalentie van DISH in de toekomst zal toenemen, niet alleen als gevolg van de vergrijzing die in de Westerse landen een steeds groter probleem wordt, maar belangrijker nog omdat DISH gerelateerd lijkt te zijn aan obesitas en diabetes mellitus type 2, aandoeningen die endemisch zijn geworden wereldwijd als gevolg van het moderne zittende leven in combinatie met een dieet hoog in vet en energie inname.[202;240]

In het tweede deel van dit proefschrift werd de morfologie van de ossificaties van DISH onderzocht, in relatie tot de biomechanica en karakteristieken van de fractuurpatronen die bij DISH worden geobserveerd. In menselijke kadaver wervelkolommen met DISH werden de oppervlaktes van de ossificaties gemeten door middel van CT scans, waaruit bleek dat de ossificaties maximaal waren op het niveau van de tussenwervelschijf en minimaal in het midden van het wervellichaam. Dit gegeven kan verklaren waarom fracturen bij DISH patiënten vaker voorkomen door het wervellichaam heen; omdat de ossificaties een solide brug vormen over de tussenwervelschijf, wordt het wervellichaam zelf de zwakste schakel in de door DISH aangedane wervelkolom.
We lieten ook zien dat de aanwezigheid van een vasculaire structuur de morfologie van de ossificaties inderdaad beïnvloedt, zoals al eerder was gesuggereerd door enkele andere auteurs.[51;65] Naarmate de oppervlakte van de ossificaties groter was, was deze verder weg van de aorta gesitueerd. Het lijkt hierdoor dat de ossificaties alleen maar plaats kunnen vinden verder weg van deze pulserende structuur. Daarnaast toonden we aan dat de VSAs consequent in het midden van het wervellichaam gelegen waren, zowel in DISH preparaten als in de controles, waar de ossificaties minimaal waren. Hoewel deze bevindingen ons niet vertellen over de causaliteit, lijkt het aannemelijk dat nieuwe botvorming niet (goed) plaats kan vinden in de buurt van een vasculaire structuur.

In het derde deel van dit proefschrift hebben we de botdichtheid van preparaten met DISH vergeleken met die van controle preparaten. We lieten zien dat de botdichtheid van het wervellichaam niet verhoogd is bij DISH preparaten door de botdichtheid van humane kadaver wervelkolommen vanuit verschillende experimentele oriëntaties te meten, waarbij de weke delen ossificaties binnen of buiten het scanveld vielen en de resultaten te vergelijken met die van controle wervelkolommen zonder DISH. We toonden aan dat de

ossificaties de botdichtheid metingen behoorlijk beïnvloedden, afhankelijk van de oriëntatie waarin de metingen verricht werden. De botdichtheid in de linker (niet-aangedane) helft van de voorachterwaartse scan verschilde niet significant van de controle preparaten. De bevindingen van deze studie geven aan dat botdichtheid metingen in DISH patiënten onbetrouwbaar kunnen zijn wanneer de weke delen ossificaties in het scanveld projecteren.

Tot slot onderzochten we of de aanwezigheid van een ankylotische wervelkolom aandoening de klinische uitkomst na een traumatische wervelfractuur beïnvloedt. Hiertoe verrichtten we een literatuuronderzoek en een retrospectief onderzoek van de gegevens van patiënten met een wervelfractuur in ons eigen ziekenhuis. We kunnen stellen dat de klinische uitkomst van patiënten met een ankylotische wervelkolom aandoening na een wervelfractuur slechter is dan in de 'normale' trauma populatie. Patiënten met een ankylotische wervelkolom aandoening worden vaker opgenomen met neurologische uitval door het ongeval, wat leidt tot hogere complicatie- en sterftecijfers. Het snel stellen van de juiste diagnose wordt bij patiënten met een ankylotische wervelkolom aandoening door een aantal dingen bemoeilijkt: zo wordt de fractuur vaak veroorzaakt door een relatief klein trauma waardoor de arts niet op een fractuur voorbereid is en kan de fractuur gemaskeerd worden door uitgebreide pathologische veranderingen op de röntgenfoto's door de aanwezigheid van AS of DISH. Omdat patiënten met een ankylotische wervelkolom aandoening vaak zeer instabiele (hyperextensie) fracturen hebben heeft operatieve stabilisatie van deze fracturen waarschijnlijk de voorkeur. En hoewel neurologische uitval na een wervelfractuur een beruchte en gevaarlijke complicatie is van langdurige AS, worden DISH en de mogelijk verstrekkende gevolgen van deze aandoening nog onderschat door veel clinici. Door de onderzoeken beschreven in dit proefschrift hebben we de kennis over deze aandoening vergroot, maar DISH verdient nog meer aandacht. Door de wereldwijde vergrijzing en de voortdurende toename van aandoeningen zoals obesitas en diabetes mellitus type 2, zal de prevalentie van DISH alleen maar toenemen in de toekomst. Clinici zouden dus voorbereid moeten zijn op een toename van het aantal (trauma) patiënten met DISH.

Dankwoord

Een proefschrift schrijven doe je niet alleen. Veel dank ben ik verschuldigd aan:

Jorrit Jan Verlaan
Cumhur Öner
Wouter Dhert
Prof. Verbout
Prof. Castelein
Jet Quarles van Ufford
Karin Thijn
Ton de Goey
Willem van Wolferen
Simon Plomp
Ronald Bleys
Marnix Lam
Wendy Scholten
Hans van Asselt
John Bemelmans
Tjitske Bosma
Tim de Wit
Paul Westers
Ingeborg van der Tweel
Mattie van Rijen
Yvonne van der Helm
Hendrik-Jan Kranenburg
Jeroen van Bemmel

De mede-bewoners van het Q-gebouw: Ruth, Joost, Joris, Fiona, Marijn, Natalja, Wouter, grote Michiel en kleine Michiel

Jossi Tijdink en Ingrid van Rooy, alias 'the Angels'

Mijn familie
Mijn echtgenoot, Martijn

Curriculum Vitae

The author of this thesis was born on March 1st in 1981 in Warnsveld, the Netherlands. In 1999 she graduated from high school (Gymnasium B, Baudartius College, Zutphen) and started to study medicine at the Utrecht University. In 2005 she performed two elective internships in Cape Town, South Africa; traumatology at the Tygerberg Academic Hospital and social medicine at METRO emergency medical cervices. During her final internship at the Department of Orthopedic Surgery of the University Medical Center Utrecht (UMCU) she commenced to investigate the prevalence of DISH in the Netherlands, which has become the basis for this thesis.

After receiving her medical degree in 2006 she worked at the Emergency Department of the UMCU for almost one year. In 2007 she started working fulltime as a research-resident under supervision of dr. J.J. Verlaan and prof.dr. F.C. Öner on the PhD project 'Diffuse Idiopathic Skeletal Hyperostosis: its prevalence, risk factors and clinical relevance', which was financed by the AO Research Fund of the AO Foundation (Davos). After working as a surgical resident (as part of the training to become an orthopedic surgeon) in the St. Antonius Hospital (Head: dr. P.M.N.Y.H. Go) for 1.5 years, which did not meet her expectations, she decided to make a career switch in March 2011. She returned to the UMCU to finish her scientific work which resulted in this thesis. Currently she is working with great fulfillment at Altrecht Mental Healthcare as a non-training resident at the Department of Acute Psychiatry.