Diffuse idiopathic skeletal hyperostosis (DISH): Is it of vascular aetiology ?

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Abstract

Objective

Reassessment of the pathological features of spinal involvement in DISH and studying the possible aetiopathogenetic mechanism/s of DISH in view of clinical, radiological and pathological findings.

Methods

Forty Egyptian patients with DISH were included in this study. They underwent clinical and radiological assessment. Routine lab tests were done in addition to measuring blood sugar, serum lipids and uric acid. Pathologic study of 50 macerated specimens of fused spines fulfilling the criteria of DISH was also performed. A pathologic study of another 50 macerated specimens from normal spines were examined as a control.

Results

Radiological assessment showed spinal involvement in 100% of the patients in the lower thoracic region, while it was present in 75%, 70% and 55% in the upper thoracic, lumbar and cervical regions respectively. Pathological study revealed a significant increase in the number and width of nutrient foramina, denoting hypervascularity of the ossified ligaments and vertebrae involved ($P < 0.001$), in addition to a significant ($P < 0.001$) increase in the size of the affected vertebrae, pointing to the possible role of a vascular disorder in the disease pathogenesis. Metabolic disorders were evident among our group of patients in the form of obesity (50%), hyperlipidemia (80%), diabetes mellitus (60%), and hypertension (45%).

Conclusion

DISH is a diffuse systemic condition which is most probably related to abnormal bone cell growth/activity reflecting the influence of metabolic factors that lead to new bone deposition. The vertebral blood supply is a predisposing factor that contributes to the onset/progression and/or localization of DISH.

Key words

Diffuse idiopathic skeletal hyperostosis (DISH), vascular, aetiology.

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Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a relatively common ossifying disorder in middle-aged and elderly people that leads to a proliferative enthesopathy, ligamentous calcification and ossification, in addition to para-articular osteophytes in both spinal and extra-spinal sites (1-4). Paleopathologic studies have identified DISH in Egyptian mummies (5), and Roman, Briton and Saxon skeletal remains (6). Further research has described it in populations derived from both North and South America, Europe, the Middle East, Africa, Australia and Asia (3). It is thus not only perhaps the oldest known rheumatic disorder, but also one of the most common. There appears to be a 2:1 male predominance in DISH with the prevalence rate in both sexes rising with age and weight (7). Approximately 12-22% of males and 12-13% of females over the age of 65 will have DISH (8).

The aetiology of DISH remains unclear. Early investigators (1, 9, 10) suggested that decreased spinal mobility plays a main role in its pathogenesis. Hence, in their view ligamentous ossification was the end result and not the cause of decreased mobility. More recent studies (11-13) reported that local growth stimulating factors may be the inciting factors for DISH development. Others considered DISH as multi-systemic hormonal disorder (14). In the meantime, there has not been full pathologic study of DISH since that published by Resnick & Niwayama in 1976 (5). Actually knowledge of the disease pathophysiology may provide opportunities for more specific targeting for disease management.

In view of the above discordant theories proposed for the disease pathogenesis, we performed this study to reassess the pathological features of spinal involvement in DISH and study the possible aetiopathogenetic mechanism/s of DISH in view of the clinical, radiological and pathological findings.

Material and methods

Patients

Forty Egyptian patients with spinal manifestations of DISH were recruited for this study. They were consecutively gathered from patients attending the Rheumatology and Rehabilitation out-patient clinic at Ain Shams University, Cairo. DISH syndrome was detected on routine radiographs of different areas of the spine. A complete history with stress laid on the symptomatology related to DISH syndrome was taken. This included stiffness, restricted range of motion, pain and dysphagia. A full history regarding joint and skin involvement was taken to exclude seronegative arthritis. Patients with a history of drug therapy in the form of vitamin A or fluoride were also excluded from this study. Special attention was given to symptoms suggestive of ischemic heart disease, diabetes mellitus and acromegaly (no patient with acromegaly was included in this study).

A complete clinical examination was performed including body weight, height, blood pressure, full articular assessment, range of motion of the back, and neurological testing in addition to examination of other systems of the body to exclude other diseases which could be related to the patient's symptomatology.

Each patient was subjected to the following laboratory tests: erythrocyte sedimentation rate (ESR by the Westergren method), complete blood count, fasting and post-prandial blood sugar, serum uric acid, serum cholesterol, triglycerides, and high density and low density lipoprotein.

Complete radiographs were taken of all patients in this study, including x-rays of the cervical, thoracic and lumbar spines anteroposterior (A.P.) and lateral views as well as x-ray pelvis A.P. view, both shoulders A.P., both knee joints A.P. and lateral views, in addition to both feet lateral view.

Radiological criteria for establishing the diagnosis of DISH include: (i) the presence of flowing calcification and ossification along the antero-lateral aspect of at least 4 contiguous vertebral bodies; (ii) the relative preservation of intervertebral disc height; and (iii) the absence of intra-articular bony ankylosis of the sacroiliac and apophyseal joints (15).

All patients included in this study met these radiologic criteria. The nature and the aim of the study were explained to all subjects included in this study and all of them gave their consent before participating.

Pathologic study

Fifty macerated specimens from fused spines meeting the DISH criteria were collected from the Anatomy Department, Faculty of Medicine, Ain Shams University (Cairo). They were sequentially identified and put aside for the purpose of this study. They were from 44 (88%) male and 6 (12%) female Egyptian subjects. Their age ranged from 50-70 years. Detailed morphological description by the naked eye was given. Special interest was devoted to the vasculature and the regional differences in the vertebrae affected. This was assessed by counting the nutrient foramina using an ocular graded scale (magnification power 10x) and was expressed as the number of nutrient foramina/cm^2. Moreover, measurement of the size of the affected vertebrae was carried out using a tape measure in two perpendicular planes (axes): the anteroposterior axis and the transverse or side-to-side axis after exclusion of the ossified ligaments. The data was expressed in the form of a Vertebral Index = antero-posterior axis/transverse axis. Plastic tape was preferred to calipers as it can better follow the vertebral surface, allowing more accurate vertebral axis measurements after exclusion of the ossified ligament.

The reproducibility of the nutrient foramina counting and vertebral size measurement was confirmed by having them calculated by two observers (the first two authors) separately. Inter-observer reproducibility was checked by using the readings of the same two observers twice, 2 weeks apart. The Kappa coefficient was calculated as a measure of the intra- and inter-observer agreement.

Longitudinal sections of the affected vertebrae were taken and examined to exclude osteoporosis. Anatomic specimens with osteoporosis had also been excluded from the study.

Plain x-rays of the specimens were taken in order to match the pathological features with the radiological ones.

Control group

Fifty specimens of normal spines were collected as a control group from the anatomy department, Faculty of Medicine, Ain Shams University (Cairo). They were all from Egyptian subjects, 50% (25) males and 50% (25) females. Their age ranged from 30-70 years. A morphological examination analogous to that carried out for the affected group was done on all the vertebrae, taking particular care with the assessment of the vertebral vasculature using the same technique and expressing the result as the number of nutrient foramina/cm^2. In addition, measurement of the size of the vertebrae was done and expressed as the Vertebral Index = anteroposterior/transverse axis. 100 normal subjects (50 men, 50 women) matched for age (51.6 ± 6.93 years) with our group of patients were collected randomly as a control group. They were subjected to thorough clinical examination, and the same radiological and laboratory investigations.

Statistical analysis

Statistical significance was assessed by Student's t-test; $P < 0.05$ was considered significant. Intra- and inter-observer agreement was assessed using the Kappa coefficient.

Results

Patients

The 40 patients ranged in age from 44 to 72 years. They included 36 men and 4 women. Most of the patients recruited for this study (22/40 or 55%) presented with a complaint of morning stiffness lasting < 30 minutes; other symptoms were pain in the spine (18/40; 45%) in either the thoracolumber region and/or the cervical region; and kyphosis (8/40; 20%). In 20% (8/40) the main presentation was extra-spinal (6 involving the foot, 1 the shoulder, 1 the knee). Dysphagia was present in 10% (4/40) of the study patients. Neurological examination was normal in all patients.

Fifty percent (20/40) of the patients were overweight (body mass index > 30) while 45% (18/40) were hypertensive (blood pressure > 140/100) and 45% (18/40) had manifestations of ischemic heart disease. Laboratory investigations showed an ESR of 3-44 mm/1st hr in the patient series. There were no significant abnormalities in the blood examinations. Table I shows the incidence of metabolic abnormalities in our patients. Hyperlipidemia manifested as elevated cholesterol (normal value (nv) ≤ 200 mg/dl) and low density lipoprotein levels (nv ≤ 150 mg/dl) with a decreased high density lipoprotein level (nv=35-60 mg/dl). Radiological studies of the patients revealed different percentages of regional involvement (Table II).

Table I. Prevalence of metabolic abnormalities in patients with DISH.

Metabolic abnormality	No. of patients	Prevalence in patient group	Prevalence in control group
Hyperlipidemia	32/40	80%	6.8%
Altered glucose tolerance (diabetes mellitus)			
Hyperuricemia	16/40	40%	6.2%

Regional radiographic findings

Thoracic Spine. Radiographs of the thoracic spine were positive in all 40 patients. Thoracic abnormalities were most frequent (100%) in the lower 5 thoracic vertebrae (7th - 12th). The upper thoracic vertebrae showed a lower incidence of abnormalities (75%; 30/40) in contrast with the lower thoracic vertebrae. Ossification appeared along the antero-lateral aspects of the vertebral bodies and continued across the disc spaces. The deposited bone varied in thickness from 1-16 mm. Radiolucent lesions in the form of a linear defect were seen in some of the vertebrae between the newly deposited bone and the adjacent vertebral body. In addition, radiolucencies within the ossified mass were also seen as a result of disc material extension. Thoracic disc space narrowing, generally mild, was present in 30% (12/40) of the patients.

Lumbar Spine. This was the second most

Table II. Segmental distribution of spinal involvement in DISH.

Spine segment	Prevalence of DISH
Cervical	55%
Upper and lower thoracic	75%
Lower thoracic	100%
Lumbar	70%

common site for DISH involvement in our patients, being present in 70% (28/40). The outgrowth ranged between 4-18 mm. The 3rd lumbar vertebral body was the most common site of abnormalities. Mild to moderate disc space narrowing was present in 40% of the affected lumbar region. In addition, radiolucent linear defects were seen in some of the vertebrae between the newly deposited bone and the adjacent vertebral body (Fig. 1).

Cervical Spine. The cervical spine was abnormal in 55% (22/40) of the patients. Abnormalities were most commonly seen in 5th and 6th vertebral bodies. Involvement of the 1st and 2nd cervical vertebrae was not seen in any of our patients. The deposited bone thickness varies between 2-12 mm. Mild to moderate disc space narrowing was noted. Also, radiolucency in the cervical region between the anterior new bone and the vertebral bodies was present. CT of the cervical vertebrae done for 4 patients with dysphagia and showed exuberant anterior osteophyte formation with calcification of the anterior spinal ligament which most likely also compressed the posterior wall of the osephagus. There was posterior osteophyte formation indenting the subarachnoid space and evidence of disc degeneration with vacuum phenomena.

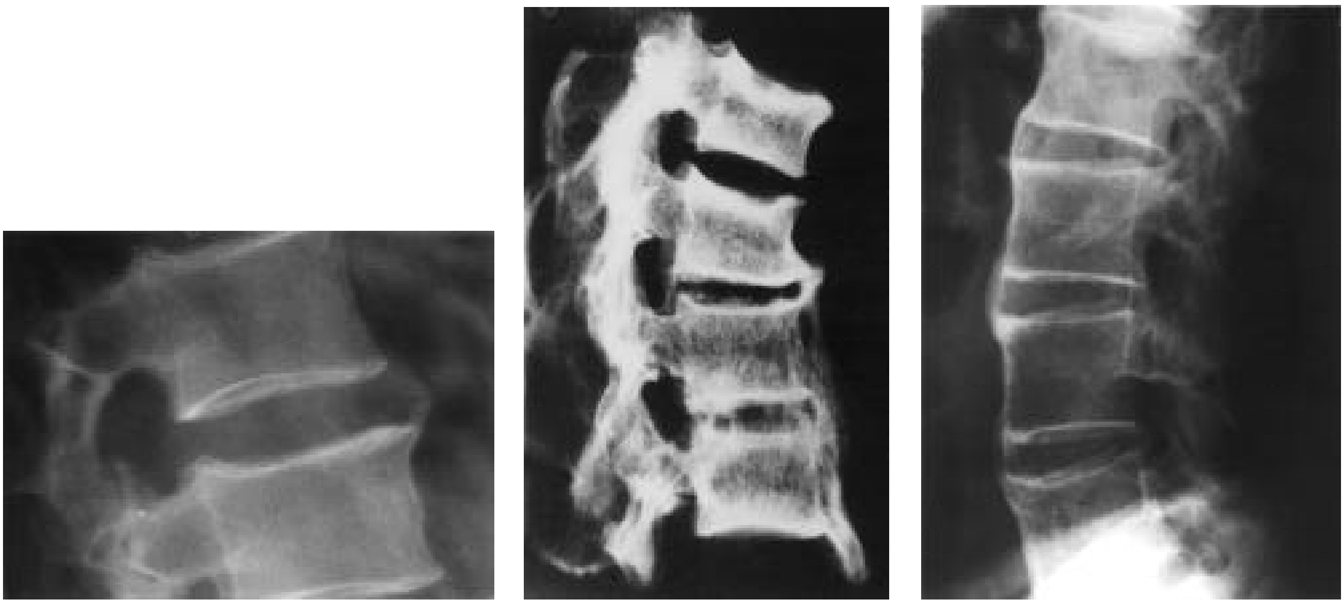
Pathological findings

The morphological features of the spinal involvement in DISH revealed interesting regional differences. Abnormalities showed a variable severity even within individual specimens; for example, severe changes might be present in the central portion of the involved segment while mild changes were noted at its periphery. The density of ossification was usually greater below than above in each of the 3 segments (thoracic, lumbar and cervical). Bony ankylosis was noted primarily in the thoracic spine, being less frequent in the lumbar and cervical regions.

Thoracic Spine. The thoracic segment was by far the most commonly involved region with a repeated picture of fused lower 6 thoracic vertebrae. Ossification of the anterior longitudinal ligament (ALL) was the earliest and most constant pathological sign. In early cases, the process of ALL ossification was found to start from the edges of two adjacent vertebrae in the direction of the disc space; giving a picture of "suture"-like indentation (Fig. 1). Complete ossification of this suture would create a single bony bridge which is at first flat, and then convex forward (excrescency). As the disease advances, the ossification sweeps into the rest of the ligament on front of the bodies, followed by the formation of more bridges and the ankylosis of more vertebrae depending upon how chronic the disease is. In its late phase, the ligament showed the characteristic "bamboo-like appearance".

Most of the specimens showed unilateral ossification of ALL on the right side with slight encroachment along the midline. The density of ALL ossification was usually greater below than above. However, in advanced lesions ossification was found to involve the left side in the same fashion as the right side, i.e. from below upward showing an ascending gradient (Figs. 2 and 3).

As regards the rest of the spinal ligaments, they were found to be much less affected and later in the disease course than the ALL. The posterior longitudinal ligament (PLL) was occasionally found to be ossified in the lower thoracic vertebrae. More posteriorly, it was interesting to find that the ligamenta flava suffered a diffuse pathological ossification along the lower 6 spines. The interspinous ligament appeared to be the only ligamentous structure to escape hyperostosis. The supraspinous ligament (SSL) showed a moderate degree of ossification. Mild lipping and ankylosis of the apophyseal joints were occasionally seen in the region from the 7th to the 9th thoracic vertebrae. Some costal facets on the bodies of the vertebrae were sur-



(a) (b) (c)

Fig. 1. (**a**) X-ray (lateral view) of the lumbar spine showing the suture-like pattern; (**b**) x-ray (dorsal view) of the dorsal spine showing the progression of anterior longitudinal ligament ossification from below upward; (**c**) x-ray (lateral view) of the lumbar spine showing the typical pattern of anterior longitudinal ligament ossification.

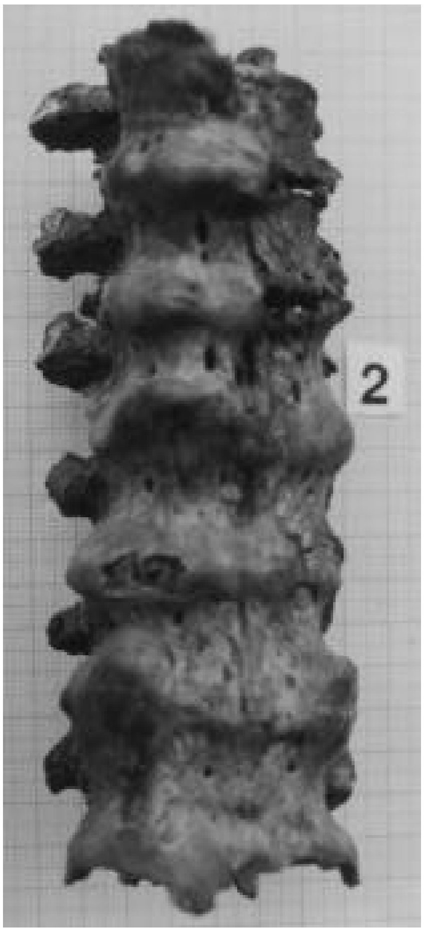


Fig. 2. A.P. view of a dorsal spine specimen showing involvement of the anterior longitudinal ligament on the right side and the start of ligament ossification on the left side from below upward.

Fig. 3. Lateral view of a dorsal spine specimen showing progression of the ossification process from below upward.

rounded by osteophytes that could protrude into the intervertebral foramina. The disc spaces were highly preserved, with occasional Schmorl's nodes on the inferior aspect of the lower thoracic vertebrae.

Interestingly, hypervascularity of the ALL and all involved vertebrae was noticed (Fig. 4). As shown in Table III there was a significantly ($P < 0.001$) increased number of nutrient foramina in the affected vertebrae compared to the control group. Furthermore, it was interesting to notice that the nutrient foramina were mainly localized at the lipping margin (Fig. 4), where the ligament starts to ossify compared to the rest of ossified ligament. Moreover, wide pore nutrient foramina were seen closer to the midline of affected vertebrae than the peripheral ones.

Table III shows also a comparison of the vertebral index between the affected vertebrae and the control vertebrae. The size of the affected vertebrae was significantly larger ($P < 0.001$) than the control group.

Studies of the reproducibility of the vertebral size measurement and of the nutrient foramina count showed high interobserver reproducibility ($\kappa = 0.92$ and $\kappa = 0.88$, respectively). Kappa values for intra-observer reproducibility were 0.91 and 0.93 (for the first and second observers, respectively) for vertebral size measurement, while they were 0.88 and 0.9 for the nutrient foramina count, indicating high reproducibility.

Lumbar Spine: Hyperostosis and ankylosis involved the lower 4 vertebrae. As in the thoracic region involvement of the ALL was more intense below than above, but the ossification was symmetrical. Plain x-rays of the specimens gave

(a)

(b)

Fig. 4. Lateral view of dorsal vertebrae showing the increased number and width of nutrient foramina (**a**), which is more prominent at the lipping margin (**b**).

Table III. Comparison and significance of markers of hypervascularity.

Variable	No. of cases	Patients (mean ± SD)	Control (mean ± SD)	P value
Vertebral index [A.P. axis (mm)/Transverse axis (mm)]	40	0.82 ± 0.677	0.67 ± 0.4615	< 0.001
Number of nutrient foramina/cm^2	40	29.65 ± 7.57	15.43 ± 4.31	< 0.001

a picture of double ribbon-like opacity with midline ossification.

As in the thoracic region, the pre-discal areas were the first to ossify in "sutures". Marked ossification was found in 4 cases in the posterior group ligaments, namely the ligamenta flava, and the interspinous and supraspinous ligaments, forming a bizarre platue-like bony mass. These ligaments could be clearly seen in the lateral view plain x-rays. The apophyseal joints were highly affected in the form of hyperostosis and ankylosis. Schmorl's nodes were only seen on the upper surface of the first lumbar vertebra. The intervertebral foramina escaped the process of hyperostosis.

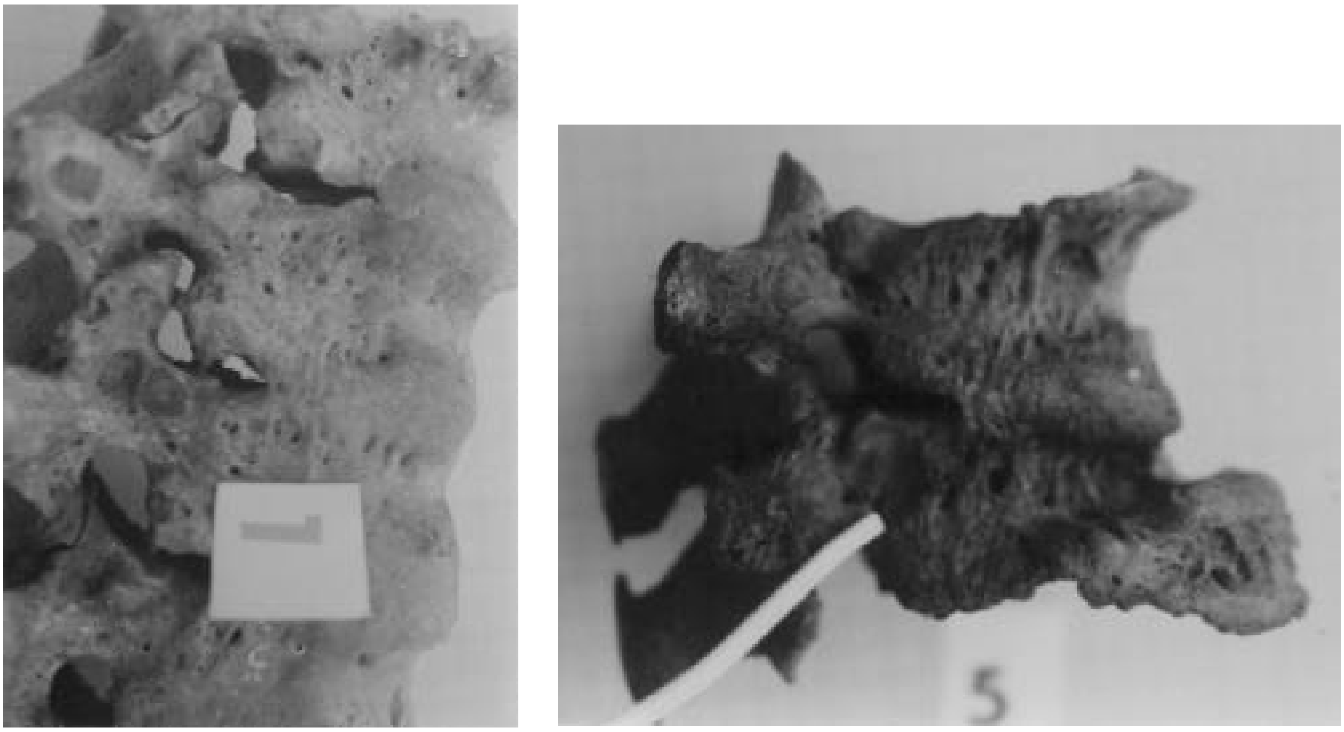
Similarly to the thoracic spine, there were multiple, prominent, wide pore nutrient foramina in the affected vertebrae and the ossified ligaments (Fig. 5a) compared to the control group. Also, the size of the affected vertebrae was significantly greater than in the control group.

Cervical Spine: The cervical spine showed manifestations of ligamentous hyperostosis in the lower 4 vertebrae. As in the other regions, ossification of the ALL was seen and bony deposition was symmetrical. Ossification of the PLL was seen and tended to be broader opposite the disc spaces. Pointed excrescences opposite the disc spaces were absent (i.e., no bamboo-like findings in the x-rays). The rest of the ligaments escaped ossification while the apophyseal joints showed mild lipping. Similar to the affected vertebrae in the thoracic and lumbar regions, the affected cervical vertebrae were significantly larger in size than in the control group, with a significantly increased number of nutrient foramina (Fig. 5b).

Discussion

Diffuse idiopathic skeletal hyperostosis (DISH) appears to be a ubiquitous skeletal condition. It was an appreciation of the diffuse nature of the condition that led to the definition of the DISH syndrome. However, the aetiology of the condition remains unknown. Researchers have studied the pathogenesis including genetic, metabolic, endocrinal and toxic factors. Investigations of HLA factors have yielded discrepant results (14). The aim of this study was to reassess the pathologic features of spinal involvement in DISH, searching for possible pathogenetic mechanism/s that could lead to its development on the basis of clinical, radiological and pathological examination.

Radiological study of the patients included in this study revealed that DISH was most prevalent in the lower thoracic region, followed by the upper thoracic and lumbar regions, and then the cervical region. Table II shows that the characteristic radiographic features of DISH were present in 100% of our patients in the lower thoracic region, in 70% in the lumbar region and in 55% in the cervical region. This is in concordance with



(a) (b)

Fig. 5. Lateral view of lumbar vertebrae (**a**) and cervical vertebrae (**b**) showing prominant, multiple nutrient foramina in the vertebrae affected and the ossified ligaments.

the previous studies published (4, 15). Resnick & Niwayama (15) reported the distribution of radiographic abnormalities in 97%, 93% and 78% in the thoracic, lumbar and cervical regions, respectively. Similarly, Oppenheimer (1), as well as EL Garf & Khater (4), reported that involvement was most frequent in the thoracic spine. In his discussion, Oppenheimer indicated that ligament ossification required two pre-existing components: disuse related to vertebral immobility and rarefaction of the adjacent bone. His observations, together with those of Leriche & Policard (9) and Smith *et al*. (10), suggested that immobilization increased the possibility of the transformation of dedifferentiated connective tissue into bone. In addition, the investigators stated that trauma was not an important aetiologic factor and that an initial decrease in spinal mobility in older patients lessened the degree of mechanical stress on the ligaments, resulting in their degeneration and ossification.

Studies of the regional differences in involvement in the upper and lower thoracic regions revealed that the lower thoracic region seems to be the most common site of involvement. Resnick & Niwayama (15) reported that thoracic abnormalities were most frequent in the 7th - 10th thoracic vertebrae; they also noted a lower incidence of abnormalities in the upper thoracic vertebrae. Based on the anatomical findings and comparing the lower thoracic vertebrae with the upper thoracic ones, the cartilage of the lower 5 ribs (false ribs) do not join the sternum. Also, the lower thoracic vertebrae have larger vertebral bodies and intervertebral discs (16). All of these factors contribute to make the lower thoracic vertebrae freer and more movable, especially in flexion and extension as movement become less restricted. In contrast, the costal cartilage of the upper 7 ribs join the sternum directly, and the vertebral bodies and intervertebral discs are smaller in size, which greatly impair the range of motion (16).

It was interesting to notice that, despite all of these factors limiting the movement of the thoracic spine, we found that the percentage of involvement in the upper thoracic spine (75%) was not significantly different from that of another well known movable area - the lumbar region (70%) - and not so much greater than that in the cervical region (55%), another highly mobile area. This suggests that the theory of immobility of the thoracic spine as a predisposing factor for DISH seems unlikely. Moreover, in agreement with our findings the most common sites of affection reported by Resnick & Niwayama (15) were L3 in the lumbar region and C5-C6 in the cervical region, which again are highly mobile sites. In addition, the extraspinal sites of DISH involvement, such as the calcanean spur and knee joint, do not support the immobility theory.

Our pathological findings agree with those of Resnick & Niwayama (15). However, although hypervascularity of the anterior longitudinal ligament was reported in their findings, we noticed hypervascularity in the vertebrae involved as evidenced by a significant ($P < 0.001$) increase in the number and width of nutrient foramina in the affected vertebrae, in addition to a significant increase in the size of the vertebrae affected compared to the control group. Reviewing the blood supply of the vertebral column, it was found that each vertebra receives several sets of nutritional vessels which consist of anterior central, posterior central, prelaminar and postlaminar branches. The first and the last of these are derived from vessels external to the vertebral column whereas the posterior central and prelaminar branches are derived from spinal branches that enter the intervertebral foramina and supply the neural, meningeal and epidural tissues as well. In the midspinal region, the internal arteries (i.e., those derived from spinal branches) provide the greater part of the blood supply to the body and vertebral arch (16). Moreover, Gutmann (17) reported that the largest blood supply in the cervical region were found between C4 and C7, while lower down the blood supply with the largest size vessels was found between T10 and L2, which is consistent with the most common sites of DISH involvement detected both radiologically and pathologically. This interesting finding raises the question of the role of the blood supply in the pathogenesis of DISH.

The possibility of osteoporosis as a cofactor for increased vasculature in the affected vertebrae has been ruled out. Moreover, an increased number and width of the nutrient foramina were seen in the affected vertebrae only compared to the non-affected ones and to the control group. However, examining cross-sections in the affected vertebrae revealed no evidence of osteoporosis. This may also be partially explained by the fact that most of our patients and most of the subjects from whom the macerated specimens were taken were males.

The higher prevalence of obesity and altered glucose tolerance recorded in our group of patients (50% and 60% respectively) agrees with the results in the literature (12, 13) which reported that between 17% and 60% of patients with DISH have impaired glucose tolerance. Controlled studies indicated that this prevalence was much higher among patients with DISH than those without the disease. Conversely, the prevalence of DISH in patients with adult onset diabetes ranges from 13% to 50% (13). Furthermore, disturbances of insulin, IGF-I and growth hormone were reported in patients with DISH (14). It was interesting also to notice the higher incidence of hyperlipidemia among our group of patients (80%), while 45% had hypertension, 45% had coronary artery disease, and 40% had hyperuricemia. The frequent association of DISH with obesity, diabetes mellitus, hyperlipidemia, hyperuricemia, hypertension and coronary artery disease does not seem to be random. We believe that the arterial blood supply of the vertebral column is the mirror that reflects the influence of these former associations on the process of new bone formation and demonstrates that DISH is an active process of ossification.

The question is: How is the ossification process is initiated and what is the link between these metabolic disorders and the process of new bone formation? The ossification process, as we found in our specimens, usually starts in the innermost layer of the ALL, at the site of the ligamentous attachment to the vertebral body, then extending to meet the other ossification arm coming from the vertebra above and/or below. We believe that this new bone formation is the result of abnormal osteoblast cell growth/activity in the bony-ligamentous region and is the clue to the pathogenesis of DISH.

But what stimulates the osteoblasts to grow in this region? It has been reported that the process of osteogenesis is promoted and maintained by several growth factors that are not even confined to bone (18). IGF-I was found to be a potent stimulator of labeled thymidine incorporation into DNA of mesodermal origin (fibroblasts) (19) and also in cultures of chondrocytes. Moreover, IGF-I was found to stimulate alkaline phosphatase activity and type II collagen in osteoblasts (20). In addition, growth hormone was found to be capable of inducing the local production of IGF-I and IGF-binding proteins in chondrocytes and osteoblasts (21). Denko *et al.* (14) reported that patients with DISH had elevated insulin and growth hormone values, which could explain the osteoblast cell growth/proliferation.

However, if there is a systemic increase of growth hormone and insulin hormone, why does DISH start in certain sites and then spread to others? We believe that hypervascularity could be the localizing value for the ossification process. This is supported by the fact that hypervasculity is important for osteoblast proliferation (18). Furthermore, in predisposed patients who suffer from hyperlipidemia, diabetes mellitus or, possibly, hyperinsulinemia, there is the increased possibility of developing atherosclerosis. It has been reported that in the earliest stages of atherosclerosis there is damage to the endothelium and aggregation of blood platelets leading to the local release of platelet derived growth factor (18), with the end result of osteoblast proliferation. However, further studies are still needed to confirm this hypothesis. Studying markers of osteoblast activity in patients with DISH is one of the options suggested.

It is difficult to tell which one leads to the other: the ossification process or hypervascularity. Recently, several reports have been published discussing the relationship between angiogenesis and ossification (19-21). Angiogenesis-stimulating activity is present in the plasma of patients with osteoarthritis and ankylosing spondylitis (19, 20). Moreover, it has been reported that during enchondral ossification, chondrocytes hypertrophy and new blood vessels grow from the perichondral vascular network, invading the cartilage (22). Osteoblastic activity then commences around the neovasculature. Interestingly, it was found that hypertrophic chondrocytes and osteoblasts each generate angiogenic factors such as transferring (23), while exogenous angiogenic factors can stimulate enchondral ossification (24). This may warrant a study of angiogenesis-stimulating activity in patients with DISH.

In conclusion, DISH is a diffuse systemic condition which is most probably related to abnormal bone cell growth/activity reflecting the influence of metabolic factors that lead to new bone deposition. The vertebral blood supply is a predisposing factor that contributes to the onset, progression and/or localization of DISH.

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References

1. OPPENHEIMER A: Calcification and ossification of vertebral ligaments: roentgen study of pathogenesis and clinical significance. *Radiology* 1942; 38: 160.
2. FORESTIER J, ROTES-QUEROL J: Senile ankylosing hyperostosis of the spine. *Ann Rheum Dis* 1950; 9: 321.
3. SMYTHE H, LITTLEJOHN G: Osteoarthritis-related conditions: DISH. *In* KLIPPEL JH and DIEPPE PA (Eds.): *Rheumatology*, Mosby, Chapter 7, Section 9, 1994.
4. EL GARF A, KHATER R: DISH, A clinico-radiological study of the disease pattern in middle eastern populations. *J Rheumatol* 1984; 11: 804.
5. MOODIE RL: *Paleopathology: An Introduction to the Study of Ancient Evidence of Disease*. Urbana University of Illinois Press, 1923; 403.
6. ROGERS J, WATT I, DIEPPE P: Arthritis in Saxon and medieval skeletons. *Br Med J* 1981; 283: 1668.
7. FORNASIER VL, LITTLEJOHN GO, UROWITZ MB: Spinal entheseal new bone formation: The early changes of DISH. *J Rheumatol* 1983; 10: 939.
8. BURKUS JK, DENIS F: Hyperextension injuries of the thoracic spine in DISH. *J Bone Joint Surg* 1994; 76-A(2): 237.
9. LERICHE R, POLICARD A: *Les Problemes de la Physiologie Normale et Pathologique de l'Os*. Paris, Masson & Cie, 1926.
10. SMITH CF, PUGH DG, POLLEY HF: Physiologic vertebral ligamentous calcification: An aging process. *Am J Roentgenol* 1955; 74: 1049.
11. ARLET J, JACQUELINE F, DEPEYRE M: Le Hanche dans l'hyperostose vertébrale. *Rev Rheum Mal Osteoartic* 1978; 45: 17.
12. LITTLEJOHH GO: Insulin and new bone formation in DISH. *Clin Rheumatol* 1985; 4: 294.
13. FORGACS SS: Diabetes mellitus and rheumatic disease. *Clin Rheumatol Dis* 1986; 12: 729.
14. DENKO CW, BOJA B, MOSKOWITZ RW: Growth promoting peptides in osteoarthritis and DISH. *J Rheumatol* 1994; 21: 1725.
15. RESNICK D, NIWAYAMA G: Radiographic and pathologic features of spinal involvement in DISH. *Radiology* 1976; 119: 559.
16. WESLEY WP: Applied anatomy of the spine. *In* ROTHMAN RH and SIMEONE FA (Eds.): *The Spine*. 3rd ed., Saunders Company, 1992; 83.
17. GUTTMANN L: Anatomical data on vertebral column and spinal cord. In: *Spinal Cord Injuries*, 2nd ed., Blackwell Scientific Publications, 1976; Chapter 1, pg. 69.
18. FAWCETT DW: *A Textbook of Histology.* 12 ed., Chapman & Hall 1994; 224-33.
19. MORELL B, FROESCH ER: Fibroblasts as an experimental tool in metabolic and hormone studies. Effects of insulin and non-suppressible insulin-like activity on fibroblasts in culture. *Eur J Clin Invest* 1973; 3: 119-23.
20. VETTER U, ZAPF J, HEIT W, HELBING G *et al.*: Human fetal and adult chondrocytes. Effects of insulin-like growth factors I and II, insulin and growth hormone on clonal growth. *J Clin Invest* 1986; 77: 1903-8.
21. NILSSON A, ISGAARD J, LINDAHL A, DAHLSTROM A, SKOTTNER A, ISAKSSON OG: Regulation by growth hormone of number of chondrocytes containing IGF-I in rat growth plate. *Science* 1986; 223: 571-4.
22. BROWN RA, WEISS JB: Neovascularisation and its role in the osteoarthritic process. *Ann Rheum Dis* 1988; 47: 881-5.
23. JONES PB, MAKKI RJ, WEISS JB: Endothelial cell stimulating angiogenesis factor - A new biological marker for disease activity in ankylosing spondylitis? *Br J Rheumatol* 1994; 33: 332-5.
24. HARADA S, NAGY JA, SULLIVAN KA: Induction of vascular endothelial growth factor expression by prostaglandin E2 and E1 in osteoblasts. *J Clin Invest* 1994; 93: 2490-9.
25. SKAWINA A, LITWIN JA, GORZYCA J, MIODONSKI AJ: Blood vessels in epiphyseal cartilage of human fetal femoral bone: A scanning electron microscopic study of corrosion costs. *Anat Embrol* 1994; 189: 457-62.
26. ALINI M, MARRIOTT A, CHEN T, ABE S, POOLE AR: A novel angiogenic molecule produced at the time of chondrocyte hypertrophy during endochondral bone formation. *Dev Biol* 1996; 176: 124-32.
27. LEVNIG M, JUAN F, GERWECK LE, JAIN PK: Effect of basic fibroblast growth factor on angiogenesis and growth of isografted bone: Quantitative *in vitro in vivo* analysis in mice. *Int J Microcirc Clin Exp* 1997; 17: 1-9.