



Diffuse idiopathic skeletal hyperostosis is associated with lumbar spinal stenosis requiring surgery

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Abstract

Factors related to the onset and progression of lumbar spinal stenosis (LSS) have not yet been identified. Diffuse idiopathic skeletal hyperostosis (DISH) increases mechanical loading on the non-fused lumbar levels and may therefore lead to LSS. This cross-sectional study aimed to identify associations between LSS and DISH. This study included 2363 consecutive patients undergoing surgery for LSS and 787 general inhabitants without symptoms of LSS as participants of the population-based cohort study, Research on Osteoarthritis/Osteoporosis Against Disability. Standing whole-spine radiographs were used to diagnose DISH based on the criteria proposed by Resnick and Niwayama. The prevalence of DISH showed a significant step-wise increase among asymptomatic inhabitants without radiographic LSS, asymptomatic inhabitants with radiographic LSS, and patients with LSS requiring surgery (14.4, 21.1, and 31.7%, respectively; $p < 0.001$). The distribution of DISH was similar between the groups, but the lower thoracic and upper-middle lumbar spine regions were more frequently involved in patients with LSS requiring surgery. Multivariate analysis indicated that DISH was an independent associated factor for LSS requiring surgery (adjusted odds ratio 1.65; 95% confidence interval 1.32–2.07) after adjustment for age, sex, body mass index, and diabetes mellitus. Among patients with LSS requiring surgery, a higher occurrence of stenosis at the upper lumbar levels and multi-level stenosis were observed in patients with DISH requiring surgery than in patients without DISH. In conclusion, DISH is independently associated with LSS requiring surgery. The decrease in the lower mobile segments by DISH may increase the onset or severity of LSS.

Keywords Diffuse idiopathic skeletal hyperostosis · Lumbar spinal stenosis · General inhabitants · Prevalence · Standing whole-spine radiographs

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Introduction

Lumbar spinal stenosis (LSS) is a chronic disease defined as the radiographic narrowing of the lumbar canal or neural foramen with encroachment on neural structures by the surrounding bone and soft tissue. LSS is also characterized by degenerated facet joints, disc protrusion, and hypertrophy of the ligamentum flavum [1]. The clinical symptoms of LSS in the elderly include impaired walking and other disabilities [1]. However, severe radiographic LSS is often observed in asymptomatic patients [2]. A population-based cohort study previously performed by our group showed that the prevalence of symptomatic LSS was only 17.5% of participants with severe stenosis, which was observed in 30.4% of the general population [3]. Although advanced age, diabetes mellitus (DM), urological disorders, hypertension,

osteoarthritis/fractures, and depressive symptoms are reportedly likely to be observed in patients with symptomatic LSS [4, 5], the triggers for LSS symptoms in patients with radiographic LSS remain unclear.

Diffuse idiopathic skeletal hyperostosis (DISH) is a non-inflammatory skeletal disease of unknown etiology characterized by calcification and ossification of soft tissues, predominantly ligaments and entheses. In DISH patients, the spinal longitudinal ligaments and entheses slowly become ossified and show decreased mobility in the affected region until complete ankylosis results [6]. DISH begins most frequently in the lower thoracic spinal segments, and later extends into the upper thoracic segments and lumbar spine [7]. The lumbosacral segment is exposed to higher mechanical stress due to fusion of thoracolumbar vertebral segments in patients with than without DISH. Therefore, DISH could be a trigger for the onset or increased severity of LSS, and some studies have indicated that mechanical stress causes accelerated ligamentum flavum hypertrophy and leads to LSS [8]. However, except in a few case reports of DISH patients who exhibited LSS [9, 10], there have been no detailed analyses of the association between LSS and DISH. Here, we hypothesized that a positive correlation exists between symptomatic LSS requiring surgery and DISH.

The aim of this study was to investigate the prevalence of DISH, using a standardized definition of DISH in a cross-sectional study, in patients with LSS requiring surgery and subjects without symptoms of LSS and to clarify the association between LSS requiring surgery and DISH using multivariate analysis that accounted for potential confounding factors.

Materials and methods

Subjects

This study included patients undergoing surgery for symptomatic LSS and general inhabitants without LSS.

Patients undergoing surgery were consecutive patients identified from the database of surgery for LSS during specific periods in which preoperative whole-spine radiographs were routinely taken at one institution (Eniwa, Hokkaido, Japan). All patients exhibited symptoms of LSS and required surgery. The surgical indications for LSS were symptoms of neurogenic intermittent claudication, intolerable leg pain or numbness refractory to conservative treatment, severe muscle weakness, or bladder or bowel dysfunction. The present study included LSS accompanied by spondylolisthesis, lumbar scoliosis, and disc herniation as well as simply degenerated facet joints, disc protrusion, or hypertrophy of the ligamentum flavum. Patients with prior spinal surgery, acute vertebral fracture, spinal malignant neoplasm, spinal

infection, general inflammatory diseases such as rheumatoid arthritis or ankylosing spondylitis, and younger patients (<50 years) were excluded. Eighteen patients were excluded because of a lack of radiographs. Fifty-two patients were excluded because of difficulty interpreting radiographs. Thus, 2363 patients were included in the present study as patients with LSS requiring surgery.

The general inhabitant participants were part of the Wakayama Spine Study, which assessed a sub-cohort drawn from Research on Osteoarthritis/Osteoporosis Against Disability (ROAD), a large-scale, prospective study of bone and joint diseases among population-based cohorts established in several communities throughout Japan [11]. We registered 1011 participants from the Wakayama Spine Study to participate in a second survey of the ROAD study, which investigated clinical and radiographic examination for LSS [3]. Participants in the Wakayama Spine Study were inhabitants of the mountainous region of Hidakagawa and the coastal region of Taiji in Wakayama. The medical history and physical examination for LSS were conducted by an experienced orthopedic surgeon (YI). Assessment of clinical symptoms was based on the definition of LSS in the North American Spine Society guidelines [12], and diagnosis of LSS required one or more of the following symptoms—pain, numbness, and neurological deficits in the lower extremities and buttocks, and bladder or bowel dysfunction. The diagnosis of LSS required that symptoms be induced or exacerbated by walking or prolonged standing and relieved by lumbar flexion, sitting, and recumbency. Radiographic LSS was defined according to the classification described in a general guideline [13], in which severe stenosis is defined as narrowing of more than two-thirds of the central area on axial magnetic resonance images. Participants with prior spinal surgery, younger participants (<40 years), and those for whom whole-spine radiographs could not be obtained were the first to be excluded from the present study. The remaining 868 participants were recruited, and 81 participants were then excluded because of symptoms of LSS. Finally, 787 participants were included as inhabitants without LSS.

Evaluation

Two authors (KY and RK), who were blinded to patient clinical information, diagnosed DISH on the basis of criteria defined by Resnick and Niwayama [7], i.e., at least four contiguous vertebral segments, preservation of intervertebral disc spaces, and the absence of apophyseal joint ankylosis or sacroiliac inflammatory changes using whole-spine radiographs. The fused vertebrae by DISH were investigated. Fifty random participants were measured twice by one author (KY) with a 1-month interval and by two authors (KY and RK) independently. Intra-class and inter-class correlation coefficients were 0.831 and 0.935, respectively.

Preoperative data, the surgical level, and surgical procedures were taken from the medical records of the patients with LSS requiring surgery. Height and body weight, which were measured on a digital scale with the participant wearing light clothing and no shoes, were used to calculate body mass index (BMI, kg/m²). DM was defined as positive in patients who were under treatment for DM or who had a hemoglobin A1c of >6.5%.

Statistical analysis

Differences between the two groups for categorical variables and continuous variables were examined using the chi-squared test and the Mann–Whitney *U* test, respectively. A *p* value of < 0.05 was considered statistically significant. To account for factors associated with symptomatic LSS, a multiple logistic regression model was used to obtain adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Factors included in the multivariate model were age, sex, BMI, DM, and DISH. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA).

Results

DISH involvement between patients with LSS requiring surgery and subjects without LSS symptoms

DISH was observed in 750 LSS patients requiring surgery and 128 inhabitants without LSS symptoms. The prevalence of DISH was significantly higher in patients with LSS requiring surgery (31.7%) than in inhabitants without LSS symptoms (16.3%) (*p* < 0.001). In addition to DISH prevalence, there were significant differences in patient

characteristics, including sex distribution, BMI, and DM between the groups (Table 1). Among inhabitants without LSS symptoms, severe radiographic LSS affecting at least one level was observed in 223 (28.4%) inhabitants. The prevalence of DISH differed significantly between inhabitants with and without severe radiographic LSS [47 (21.1%) and 81 (14.4%) cases, respectively; *p* = 0.023] (Fig. 1).

Figure 2 shows the distribution of DISH-affected vertebrae in patients with LSS requiring surgery and inhabitants without LSS. The distribution of DISH-related vertebral fusion was similar, exhibiting a platykurtic distribution between the two groups. However, fused vertebrae by DISH

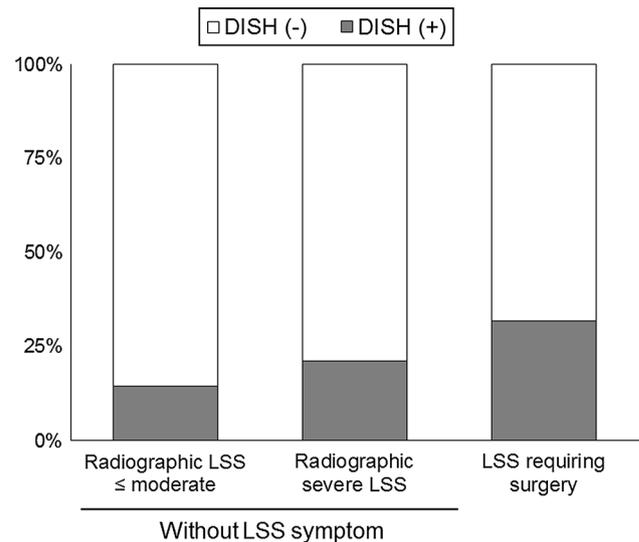


Fig. 1 Prevalence of diffuse idiopathic skeletal hyperostosis (DISH). The prevalence of DISH differed significantly among asymptomatic inhabitants without radiographic lumbar spinal stenosis (LSS) (14.4%), asymptomatic inhabitants with severe radiographic LSS (21.1%), and patients with LSS requiring surgery (31.7%) (*p* < 0.0001)

Table 1 Characteristics of sample groups at each institution

Variable	LSS patients requiring surgery	General inhabitants without LSS symptom	<i>p</i> value
Location of Institution	Eniwa, Hokkaido	Wakayama, Kinki	
Investigation period	2002–2010	2008–2010	
Total number	2363	787	
Population	Preoperative LSS patients	General population	
Male sex, <i>n</i> (%)	1,177 (49.8)	263 (33.4)	< 0.001*
Age, mean (SD)	68.0 (8.4)	67.2 (12.4)	0.942**
BMI, mean (SD)	25.0 (3.5)	23.2 (3.5)	< 0.001**
DM, <i>n</i> (%)	395 (16.7)	39 (5.0) ^a	< 0.001*

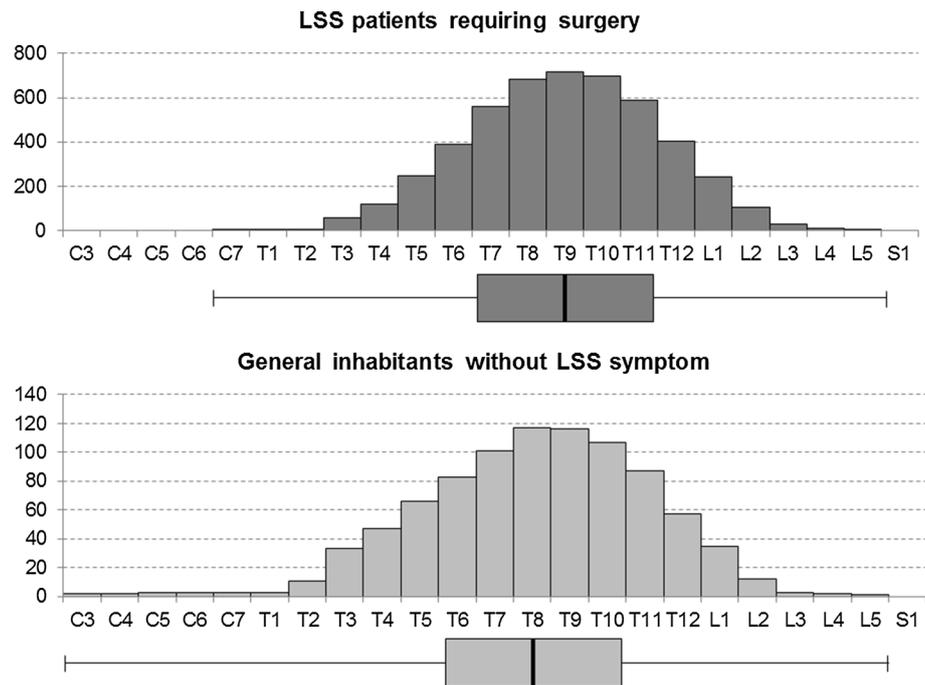
LSS lumbar spinal stenosis, SD standard deviation, BMI body mass index, DM diabetes mellitus

*Chi-squared test

**Mann–Whitney *U* test

^aTwo patients were missing data on DM

Fig. 2 Distribution of fused vertebrae resulting from diffuse idiopathic skeletal hyperostosis (DISH) at each institution. The box plot represents the sample minimum, the lower quartile or first quartile, the median, the upper quartile or third quartile, and the sample maximum for each group. The distribution of DISH was similar, but the median and quartile were more distal in patients with lumbar spinal stenosis (LSS) requiring surgery than in inhabitants without LSS symptoms (T9 vs T8, respectively; $p < 0.001$). The number of segments fused by DISH was not different between the two groups



were observed significantly more caudally in patients with symptomatic LSS than in general inhabitants (median T9 and T8, respectively; $p < 0.001$). The number of fused segments (mean \pm standard deviation) did not differ significantly (symptomatic LSS 6.49 ± 2.50 ; inhabitants without LSS 6.94 ± 3.17 ; $p = 0.367$).

Comparison between patients with LSS requiring surgery and subjects without LSS symptoms

To investigate LSS requiring surgery and DISH, multivariate analysis was performed with adjustment for potential confounders (age, sex, BMI, and DM). Multiple logistic regression analysis showed that male sex (aOR 1.66; 95% CI 1.39–1.98), a higher BMI (aOR 1.15; 95% CI 1.12–1.18), DM (aOR 3.09; 95% CI 2.18–4.37), and DISH (aOR 1.65; 95% CI 1.32–2.07) were independent risk factors for LSS requiring surgery (Table 2).

Association between DISH and decompression levels in patients with LSS requiring surgery

The association between DISH-affected lower-end vertebrae and stenotic levels was investigated in patients with LSS requiring surgery. The decompression levels at the time of surgery were investigated as the stenotic levels because all surgeries involved decompression with or without additional fusion for stenosis.

Figure 3a shows the differences between patients with and without DISH with respect to decompression levels. The L4–5 level was the most prominently affected level in both

Table 2 Multivariate analysis of associated factors for LSS requiring surgery

Variable	aOR	<i>p</i>	95% CI
Male sex	1.656	< 0.001	1.385–1.980
Age, 1-year increase	1.003	0.442	0.995–1.012
BMI, 1-unit increase	1.149	< 0.001	1.119–1.180
DM positive	3.088	< 0.001	2.183–4.367
DISH positive	1.649	< 0.001	1.317–2.065

Multiple logistic regression analysis was performed with adjustments for sex, age, BMI, DM, and DISH

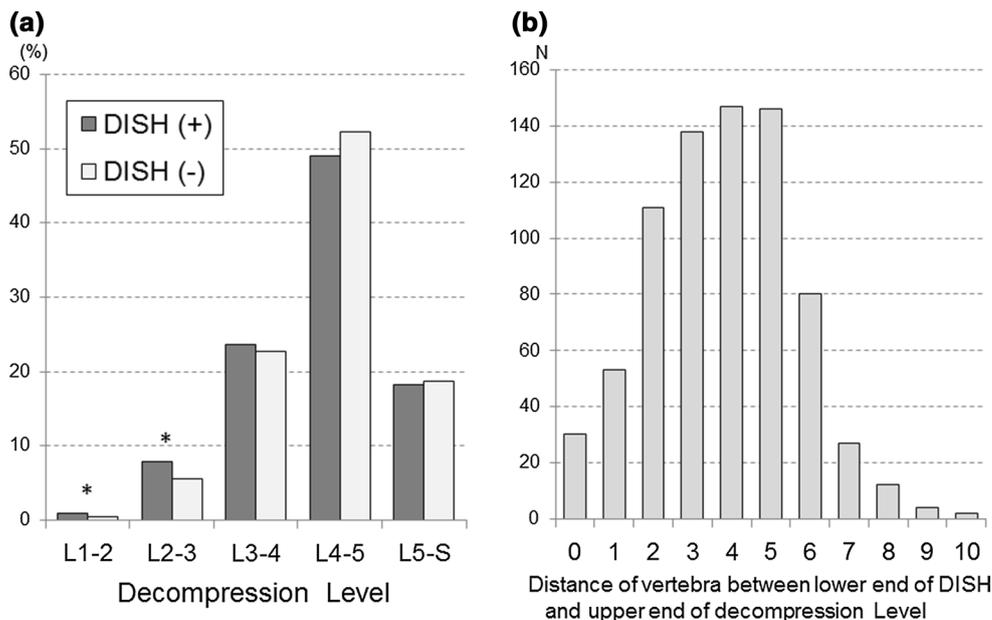
aOR adjusted odds ratio, CI confidence interval, BMI body mass index, DM diabetes mellitus, DISH diffuse idiopathic skeletal hyperostosis

groups; however, decompression was more often performed for upper lumbar lesions (L1–2 and L2–3) in patients with than without DISH ($p < 0.001$). Moreover, multi-level stenosis requiring decompression of three or more levels was more frequent in patients with DISH (169 patients, 39.2%) than without DISH (581 patients, 30.0%; $p < 0.001$). Figure 3b shows that stenosis immediately distal to the fused vertebra was observed in 30 of 750 patients (4%).

Discussion

The present study revealed that DISH is independently associated with LSS requiring surgery. DISH was first described by Forestier and Rotes-Querol [14], at which time the disease was called senile ankylosing hyperostosis. DISH is

Fig. 3 a Ratio of each lumbar level requiring decompression between patients with and without diffuse idiopathic skeletal hyperostosis (DISH). Decompression surgery at L1–2 and L2–3 was performed more frequently in patients with than without DISH ($p < 0.001$). **b** Distribution of distance of vertebra between lower end of DISH and upper end of decompression level. The segment immediately distal to DISH (distance = 0) required decompression in 30 of 750 patients (4%)



currently diagnosed based on the classification criteria established by Resnick and Niwayama [7]. The complications of DISH include unstable spinal fractures, dysphagia, postsurgical heterotopic ossification, difficult intubation, difficult gastroscopy, aspiration pneumonia, and myelopathy [15, 16]. Although we could not evaluate cause and effect in this cross-sectional study, LSS cannot cause DISH as a noninflammatory skeletal disease. Therefore, our results show that LSS is a complication of DISH in terms of onset or increased severity. To the best of our knowledge, this is the first study to investigate associations between DISH and LSS in a large population while adjusting for multiple confounding factors.

Although the mechanism of the positive association between DISH and LSS is still unclear, a likely reason is the increased mechanical load secondary to DISH-induced spinal segment fusion. Fractures of an ankylosed spine in patients with DISH tend to be unstable even after low-energy impact and can result in neurological deficits compared with a normal spine [16]. These poor clinical outcomes after trauma are believed to be caused by the development of long lever arms in the spinal column, upon which forces can act during trauma, resulting in instability of the fracture site/non-fused segments caused by ossification of supportive and elastic soft tissues. Meanwhile, DISH-induced spinal segment fusion may also chronically magnify the biomechanical load at the non-fused segment, as in patients with acute spinal trauma. Therefore, the increased stress associated with hypermobility of the non-fused spinal segment in patients with DISH could cause disc degeneration or hypertrophy of the ligamentum flavum and lead to LSS. The step-wise increase in the

prevalence of DISH among the study participants (asymptomatic inhabitants without radiographic LSS, 14.4%; asymptomatic inhabitants with severe radiographic LSS, 21.1%; and patients requiring surgery for LSS symptoms, 31.7%) supports our hypothesis in one aspect.

A few patients in the present study required decompression immediately distal to the segment affected by DISH-induced fusion. The most affected stenotic levels were the lower lumbar segments which were generally exposed to the highest stress during postural changes [17, 18], even in patients with DISH. However, a higher occurrence of stenosis at the upper lumbar levels and multi-level stenosis were observed in patients with than without DISH among patients with LSS requiring surgery. This tendency may indicate that the presence of fewer mobile intervertebral segments in the middle-lower lumbosacral spine increases the potential for the development of LSS requiring surgery because of greater mechanical loading.

Kyphosis may play a role in LSS manifestation and presentation. Hirano et al. [19] found that patients with kyphotic posture were more likely to have symptomatic LSS. Kyphosis of the thoracic or lumbar spine has frequently been observed in patients with DISH [10, 20]. When considering these reports and the results of the present study, the increased mechanical stress in patients with DISH might trigger LSS symptoms in patients with radiographic LSS, coupled with kyphotic spinal alignment.

Recent studies have also suggested an association between several genetic factors (COL6A, FGF2, or ENT1), with DISH [21, 22]. Although an association between these genes and the development of LSS has not been reported, future studies may identify the gene common to both

abnormal ossification and LSS, but the clinical and basic mechanisms will also need to be clarified.

The reported prevalence of DISH varies widely, from 2.9–39% [10, 23–26]. This wide range may be due to differences among investigated populations and screening methods.

Prior studies have associated DISH with demographic and metabolic factors such as race [23, 24], male sex [10, 23, 24, 26], advanced age [10, 23, 24, 26], obesity [14, 27], and DM [27]. We previously evaluated patients for LSS using whole-spine radiographs and found the greatest prevalence of DISH (52/132 participants, 39.4%) in LSS patients who were aged ≥ 40 years [10]. The prevalence in the previous study was greater than 10.8%, which was shown in our report of the first survey of the ROAD study that also used whole-spine radiographs in the Japanese general population (without evaluation for LSS) [26]. However, in the previous study, the number of participants was too small for the prevalence of DISH to be determined. In the present study, we investigated a sufficient number of patients with LSS at one institution and confirmed a high prevalence (31.7%) of DISH in patients with LSS. Furthermore, we directly compared that result with the prevalence in the general population without LSS, detected in the Wakayama Spine Study, to confirm that DISH had a positive influence on symptomatic LSS with adjustment for potential confounding factors.

The majority of reports used lateral chest radiographs to diagnose DISH [23, 24]. Although Mata et al. [28] demonstrated high reliability of chest radiographs for the diagnosis of DISH, chest radiographs cannot evaluate the cervical or lumbar region. A whole-spine radiograph can evaluate all spinal segments except lower cervical to upper thoracic, which are obscured by the scapulae or humeral heads. The reliability for the diagnosis of DISH was almost perfect in this study (intra- and inter-class correlation coefficients of 0.831 and 0.935, respectively). Therefore, the prevalence of DISH demonstrated in this study can be considered accurate with respect to past reports.

There were several limitations to this study. First, the severity of LSS was not considered in the analysis because the evaluation of severity of LSS differed by institution. Although the Wakayama Spine Study included the modified Zurich Claudication Questionnaire to evaluate the severity of LSS, the sample size of symptomatic LSS patients in the general population ($n = 81$) was too small to allow a relationship between DISH and LSS symptom severity to be determined. This could be addressed in a larger study. Second, several factors associated with LSS symptom severity, including spinal disorders such as spondylolisthesis [29], degenerative scoliosis [1] or psychological factors [5], were not included in this study. Although no study has investigated the association between DISH and depression, the psychological status of the patients can affect the results.

Future studies should include these confounders through a matched case–control design. Third, there were geographical differences in this study. The patients with LSS requiring surgery were recruited from all over Hokkaido, whereas the participants from the general population were recruited from Wakayama. Racial and ethnic differences have been suggested as important predisposing factors for DISH [23, 24]. The race and culture between Hokkaido and Wakayama are almost identical, but the food differs slightly because the distance between these two regions is approximately 1200 km. To confirm the reproducibility in a different regional setting, the same analyses were conducted between the general population without LSS in Wakayama and patients with LSS requiring surgery in Osaka, which is located near Wakayama in the Kinki region of central Japan. This analysis provided the same result regarding the impact of DISH on LSS, i.e., DISH was an independent associated factor for LSS requiring surgery (Supplemental data 1). Hence, the effect on the results of the regional difference seen in the present study is likely negligible.

In conclusion, this is the first report to demonstrate a significant association between the presence of DISH and LSS requiring surgery. DISH was an independent associated risk factor for LSS requiring surgery after adjustment for age, sex, BMI, and DM. The decrease in the number of mobile segments caused by DISH-induced vertebral fusion may increase the onset or severity of LSS. DISH is diagnosed not only by orthopedic surgeons and neurologists, but also by rheumatologists and general practitioners using plain radiographs. Thus, an awareness of the high prevalence of LSS in patients with DISH can lead to early diagnosis and treatment.

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Compliance with ethical standards

Conflict of interest This study was supported by Grants-in-Aid for Scientific Research (B20390182, B23390357, B26860419, C20591737, C20591774, and C26462249), for Young Scientists (A18689031), and for Exploratory Research (19659305) from the Japanese Ministry of Education, Culture, Sports, Science and Technology; H17-Meneki-009, H18-Choujyu-037, and H20-Choujyu-009 from the Ministry of Health, Labour and Welfare; Research Aid from the Japanese Orthopaedic Association; Grants from the Japanese Orthopaedics and Traumatology Foundation, Inc. (nos. 166 and 256); and a Grant-in-Aid for Scientific Research (C22591639) from the Japanese Society for the Promotion of Science. The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. Funding was provided by the Japan Osteoporosis Society and Wakayama Medical Award for Young Researchers.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards in the Wajokai Eniwa Hospital and Wakayama Medical University.

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